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(19)

(54) PYRROLIDONES AND PROCESS FOR THEIR MANUFACTURE

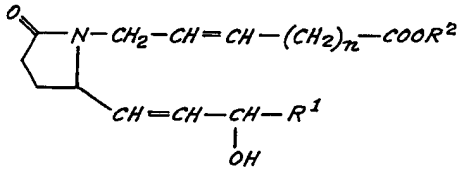
(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt/Main 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to pyrrolidones and to a process for their manufacture.

Prostaglandins are a group of natural substances which have been isolated from various animals tissues. In mammals, they are responsible for a variety of physiological effects. Natural prostaglandins have a hydrocarbon skeleton generally containing 20 carbon atoms and differ predominantly from one another in the number of hydroxy groups and double bonds present in the cyclopentane ring (as to the structure and activity of prostaglandins, see inter alia M. F. Cuthbert "The Prostaglandins, Pharmacological and Therapeutic Advances", William Heinemann Medical Books Ltd., London (1973)).

Prostanoic acid analogues which do not occur naturally and in which the great variety of pharmacological effects of natural prostanoic acids is differentiated, and methods for their production, are gaining increasing importance.

The present invention provides pyrrolidones which have the general formula I



(I)

in which

R^1 represents a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical having up to 10 carbon atoms, or a cycloaliphatic hydrocarbon radical having 3 to 7 carbon atoms, which radicals may be unsubstituted or substituted by one or more of the following:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 5 carbon atoms,

b) a phenoxy group which may carry one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms, optionally halogenated phenoxy groups, and alkoxy groups of 1 to 4 carbon atoms,

c) a furyloxy, thienyloxy or benzyloxy group which may carry, in its nucleus, one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms, and alkoxy groups of 1 to 4 carbon atoms,

d) a trifluoromethyl or pentafluoroethyl group,

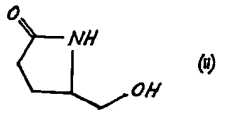
) a cycloalkyl group of 3 to 7 carbon atoms,
f) a phenyl, thienyl or furyl group which may carry one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms, and alkoxy groups of 1 to 4 carbon atoms,

R^2 represents a straight or branched chain, saturated or unsaturated, aliphatic or cycloaliphatic hydrocarbon radical having up to 6 carbon atoms, or an araliphatic hydrocarbon radical having 7 or 8 carbon atoms, and n represents the integer two, three or four, as well as the corresponding free acids and the salts, especially the physiologically acceptable e.g. metal or amine, salts thereof.

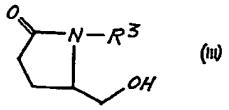
When two or more substituents are present, they may be the same as each other or different.

a_1) a pyrrolidone of the formula II

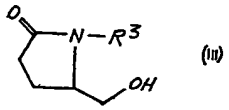
The present invention further provides a process for the manufacture of a pyrrolidone of formula I, wherein


(II)

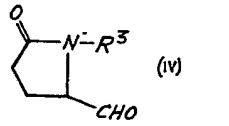
is protected at the nitrogen atom by introducing a protective group (R^3), which can easily be split off, thus yielding a pyrrolidone of the formula III


(III)

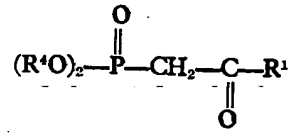
a_2) a pyrrolidone of the formula III


(III)

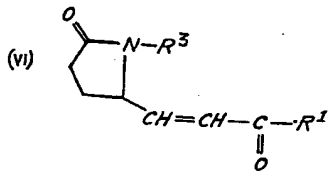
is oxidized to yield an aldehyde of the formula IV


(IV)

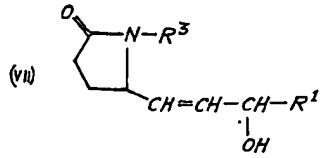
a_3) the so-obtained aldehyde of formula IV is reacted with a phosphonate of the formula V


V

in which R^1 is defined as above, and R^4 represents an unbranched alkyl group of 1 to 4 carbon atoms, to yield a compound of the formula VI


(VI)

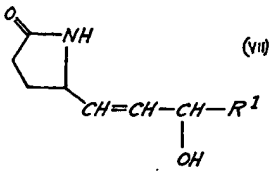
a_4) in the so-obtained compound of formula VI, the keto-carbonyl group is reduced to yield a compound of the formula VII



(VII)

in which R^1 is defined as above,

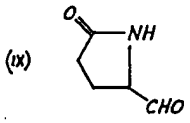
a_5) in the compound of formula VII, the protective group linked to the nitrogen atom is split off to yield a compound of the formula VIII



(VIII)

in which R^1 is defined as above, or

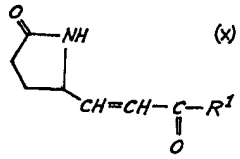
a_{5_1}) the pyrrolidone of formula II is oxidized to yield an aldehyde of the formula IX



(IX)

$a_{5_{1'}}$) the protective group linked to the nitrogen atom of the aldehyde of formula IV is split off to give an aldehyde of formula IX,

a_{5_2}) the so-obtained aldehyde of formula IX is reacted with a phosphonate of formula V to yield a compound of the formula X



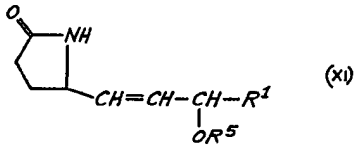
(X)

in which R^1 is defined above, or

$a_{5_{2'}}$) in a compound of formula VI, the protective group linked to the nitrogen is split off to yield a compound of formula X,

a_{5_3}) in a compound of formula X, the ketocarbonyl group is reduced to yield a compound of formula VIII,

a_6) the alcohol function in a compound of formula VIII is protected with a group, which can easily be split off, under acid conditions, to yield a compound of the formula XI



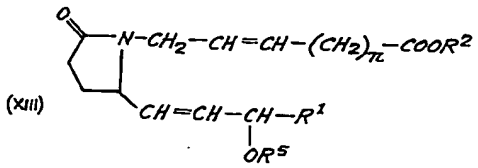
(XI)

in which R^1 is defined as above, and R^5 represents a protective group, which can be easily split off under acid conditions,

a_7) the pyrrolidone of formula XI is deprotonized by means of a base at the nitrogen atom, and the thus-formed anion is reacted with a carboxylic acid derivative of the formula XII

$$Y—CH_2—CH=CH—(CH_2)_n—COOR^2 \qquad XII$$

in which R^2 and n are defined as above, and Y represents a radical which can be substituted by a nucleophilic substitution reaction, to yield a compound of the formula XIII



(XIII)

in which R^1, R^2 and n are defined as above, and R^5 represents a protective group, which can easily be split off under acid conditions, the resulting ester is optionally hydrolyzed to yield the corresponding acid of formula XIII, in which R^2 represents hydrogen,

a_8) the alcohol protective group R^5 in the compound of formula XIII is split off to yield a compound of formula I, and optionally this compound is converted into the corresponding free acid or a salt thereof, or

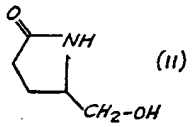
$a_{8'}$) the compound of formula VIII is deprotonized by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield a compound of formula I directly, or

a_{7_1}) the pyrrolidone of formula XI is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII in which R^2 represents hydrogen, to yield a compound of formula XIII in which R^2 represents hydrogen, and the resulting acid is optionally converted into an ester of formula XIII, and step a_8) is carried out, or

a_{8_1}) the alcohol protective group in the compound of formula XIII in which R^2 represents hydrogen, is split off to yield a compound of formula I, in which R^2 represents hydrogen, and this acid is optionally converted into a salt or an ester thereof, or

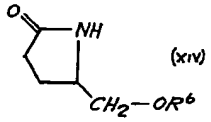
$a_{8_{1'}}$) the compound of formula VIII is deprotonized by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 represents hydrogen, to yield directly a compound of formula I in which R^2 represents hydrogen, or

b_1) into the pyrrolidone of formula II



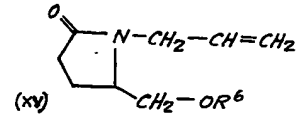
(II)

an alcohol protective group R^6, which can easily be split off under acid conditions, is introduced to yield a compound of the formula XIV



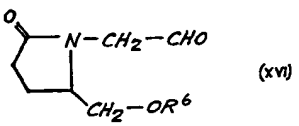
(XIV)

b_2 the pyrrolidone of formula XIV is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with an allyl halide to yield a pyrrolidone of the formula XV



(XV)

b_3) the so-obtained pyrrolidone of formula XV is ozonolyzed to yield an aldehyde of the formula XVI

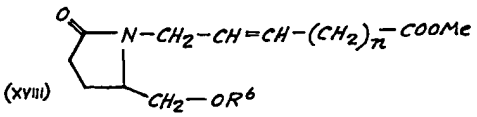


(XVI)

b_4) the so-obtained aldehyde of formula XVI is reacted with an ylide of the formula XVII

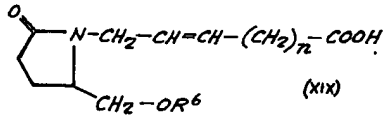
$$(R^7)_3P=CH(CH_2)_nCOOMe \qquad \text{XVII}$$

in which n is defined as above, R^7 represents identical or different groups selected from straight-chain alkyl groups of 1 to 4 carbon atoms and phenyl groups, and Me represents an alkali metal atom, to yield a compound of the formula XVIII



(XVIII)

and this compound is treated to set free the corresponding acid of the formula XIX

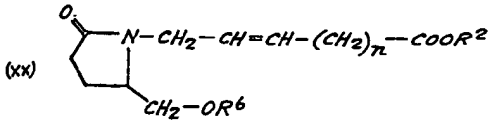


(XIX)

in which formulae n is defined as above, or

$b_{4'}$) the protected pyrrolidone of formula XIV is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 represents hydrogen, to yield a compound of formula XIX,

b_5) the so-obtained compound of formula XIX is converted into the corresponding ester of the formula XX

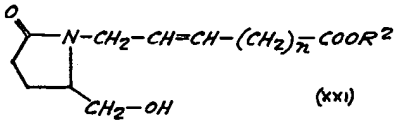


(XX)

in which R^2 and n are defined as above, or

$b_{5'}$) the protected pyrrolidone of formula XIV is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield the compound of formula XX directly,

b_6) the protective group R^6 in the so-obtained compound of formula XX is split off under acid conditions to yield an alcohol of the formula XXI



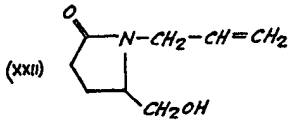
(XXI)

in which R^2 and n are defined as above, and then the corresponding acid may optionally be set free, or

$b_{6'}$) esterification of a compound of formula XIX and splitting-off of the protective group R^6 are carried out in a single step, or

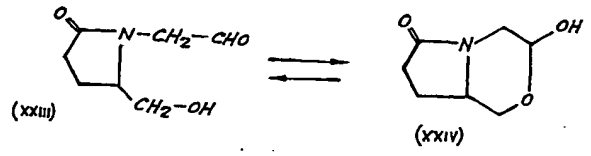
$b_{6''}$) the pyrrolidone of formula II is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield a compound of formula XXI directly, or

b_{6_1}) the pyrrolidone of formula II is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with an allyl halide to yield a compound of the formula XXII



(XXII)

b_{6_2}) The so-obtained compound of formula XXII is ozonolyzed to yield a compound of the formula XXIII and/or its cyclisized tautomer of the formula XXIV

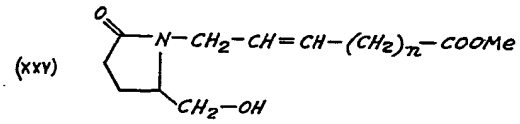


(XXIII) (XXIV)

or

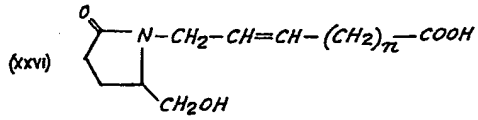
$b_{6_{2'}}$) the protective group R^6 is split off from a compound of formula XVI also to yield the compounds of formulae XXIII and/or XXIV,

b_{6_3}) the compounds of formulae XXIII and/or XXIV is or are reacted with an ylide of formula XVII to yield a compound of the formula XXV



(XXV)

and the corresponding acid of the formula XXVI



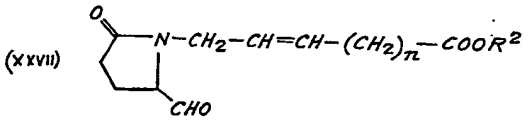
(XXVI)

is set free therefrom and optionally converted into an ester of formula XXI, in which formulae XXV and XXVI n is defined as above, or

$b_{6_{3'}}$) the pyrrolidone of formula II is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 represents hydrogen, or

$b_{6_{3''}}$) the protective group R^6 is split off from a compound of formula XIX to a compound or formula XXVI,

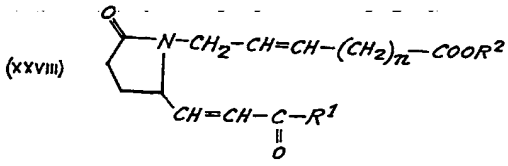
b_7 the so-obtained alcohol of formula XXI is oxidized to yield an aldehyde of the formula XXVII



(XXVII)

in which R^2 and n are defined as above, and optionally the corresponding acid of formula XXVII (R^2=H) is set free therefrom,

b_8) the so-obtained aldehyde of formula XXVII is reacted with a phosphonate of formula V to yield a compound of the formula XXVIII



(XXVIII)

in which R^1, R^2 and n are defined as above, or

$b_{8'}$) a compound of formula X is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield a compound of formula XXVIII directly,

b_9) in the so-obtained compound of formula XXVIII, the ketocarbonyl group is reduced to yield a compound of formula I, and this compound is optionally converted into the free acid or a salt thereof, or

b_{7_1}) a compound of formula XXVI is oxidized to yield an aldehyde of formula XXVII, in which R^2 represents hydrogen, and this is optionally converted into an ester of formula XXVII,

b_{8_1}) an aldehyde of formula XXVII, in which R^2 represents hydrogen, is reacted with a phosphonate of formula V to yield a compound of formula XXVIII, in which R^2 represents hydrogen, and this is optionally converted into an ester of formula XXVIII, or

$b_{8_{1'}}$) a compound of formula X is deprotonized at the nitrogen atom by means of a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 represents hydrogen, directly to yield a compound of formula XXVIII, in which R^2 represents hydrogen,

b_{9_1}) in a compound of formula XXVIII, in which R^2 represents hydrogen, the ketocarbonyl group is reduced, and the resulting compound of formula I, in which R^2 represents hydrogen, is optionally converted into a salt or an ester thereof.

Among the meanings given for the substituents R^1, R^2 and n, the following are preferred: For

R^1 a straightchain or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical having up to 7 carbon atoms, or a cycloaliphatic hydrocarbon radical having 5 to 7 carbon atoms, which radicals may be unsubstituted or substituted by one or more of the following:

a) a straightchain or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 4 carbon atoms,

b) a phenoxy group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, optionally halogenated phenoxy groups and alkoxy groups of 1 or 2 carbon atoms,

c) a thienyloxy or benzyloxy group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, and alkoxy groups of 1 or 2 carbon atoms,

d) a trifluoromethyl group,

e) a cycloalkyl group of 5 to 7 carbon atoms,

f) a phenyl or thienyl group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms and alkoxy groups of 1 or 2 carbon atoms, for

R^2 a straight or branched chain alkyl group of 1 to 6 carbon atoms, a straight or branched chain alkenyl group of 2 to 4 carbon atoms, a cycloalkyl group of 5 or 6 carbon atoms, or an aralkyl group of 7 or 8 carbon atoms.

Particularly preferred are the following substituents for

R^1 a straight or branched chain alkyl group of 1 to 7 carbon atoms, a straight or branched chain alkenyl group of 3 to 5 carbon atoms, or a cycloalkyl group of 5 to 7 carbon atoms, which may be substituted by one or more of the following:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 3 carbon atoms,

b) a pheoxy group which may carry one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and optionally chlorinated or fluorinated phenoxy groups,

c) a thienyloxy or benzyloxy group which may carry in its nucleus one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

d) a trifluoromethyl group,

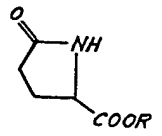
e) a cycloalkyl group of 5 to 7 carbon atoms,

f) a phenyl or thienyl group which may carry one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms; for

R^2 a straight chain alkyl group of 1 to 6 carbon atoms, a branched chain alkyl group of 3 to 5 carbon atoms, a straight chain alkenyl group of 2 to 4 carbon atoms, a cyclopentyl or cyclohexyl group, or a benzyl group, and for n the integer 3.

The hydroxymethyl-pyrrolidone of formula II, used as a starting material in the process of the invention, may be prepared according to methods known in the art (cf. J. Amer. Chem. Soc. *74*, p. 851, (1952)).

For this purpose, a glutamic acid is refluxed for some hours in the presence of an alcohol ROH and an acid catalyst t yield the 5-alkoxycarbonyl-pyrrolidone-(2) of the formula XXIX



(XXIX)

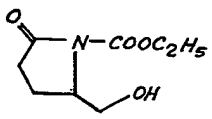
in which R is defined as above.

This reaction can especially advantageously be carried out using concentrated sulfuric acid as a catalyst and *n*-butanol as the alcoholic component, since the reaction water can be separated by means of a water separator during the reaction.

The conversion of a compound of formula XXIX into a compound of formula II by catalytic hydrogenation is also disclosed in J. Amer. Chem. Soc. *74*, p. 851 (1952). As the catalyst suitable for the hydrogenation, any one of numerous metals and noble metals, for example, Raney nickel, copper chromium oxide and ruthenium oxide on carbon, may be used. The hydrogenation reaction is generally carried out at 100—250°C, preferably at 140—180°C, under a pressure of 150 to 250 atmsg., in a suitable solvent, preferably an alcohol, for example, methanol, ethanol or isopropanol, or an ether, for example, tetrahydrofuran or dioxane.

The process of the invention mentioned sub (a) starts by introducing the protective group R^3 at the nitrogen atom; this may be done, however, at practically any stage preceding the alkylation reaction proper. The protective group may generally be split off at any stage preceding the alkylation reaction, but advantageously at the last step preceding the introduction of the carboxy side chain.

The protective group may best be introduced into the compound of formula II, preferably by converting the lactam into the corresponding carbamic acid ester, for example by means of chloroformic acid ethyl ester under alkylating conditions, for example an alcoholate in ethyl alcohol, sodium amide in benzene or toluene, potassium hydroxide in dimethylsulfoxide. From the compound of formula II, for example a compound of the formula XXX



(XXX)

is then obtained.

Further protective groups which may be used are, for example, the benzyl group, the tert.-butyl group, the trimethyl-silyl group or the formyl group.

The oxidation of the compound of formula III yielding the compound of formula IV may be carried out using an oxidizing agent as currently used for the oxidation of aliphatic alcohols to aldehydes. Some methods are disclosed in Houben-Weyl, Vol. 7/1, page 159. Further suitable oxidants are the complex compounds obtained from thio-ethers, for example, dimethylsulfide or thioanisole with chlorine or N-chlorosuccinimide (cf. J. Amer. Chem. Soc. *94*, p. 7586 (1972), J. Org. Chem. *38*, p. 1233 (1973)). Furthermore, an oxidation with dimethylsulfoxide under various conditions is also applicable (cf Chem. Rev. *67*, p. 247 (1967)).

An especially preferred process is the oxidation with the complex compound of chromium trioxide and pyridine which is prepared in an inert solvent, preferably methylene chloride, and then mixed with a solution of the alcohol of formula III at −20 to +20°C. The oxidation is speedy and is generally complete after 5 to 45 minutes, when following the indications given in J. Org. Chem. *35*, page 4000 (1970), or J. Org. Chem. *26*, page 4814 (1961). The aldehyde of formula IV may be used without further purification for the next reaction step, or, where required, may be purified by column chromatography.

The reaction of the phosphonate of formula V with the compound of formula IV may be carried out under the conditions usual for the Horner reaction, for example in an ether at room temperature. As the ether, there is preferably used diethyl ether, tetrahydrofuran or dimethoxyethane. The phosphonate is preferably used in an excess, to ensure a complete reaction.

The reaction is generally complete after 1 to 5 hours at room temperature. The reaction product is generally isolated and purified by the usual methods. Details concerning the handling of this reaction are given in J. Amer. Chem. Soc. *83*, p. 1733 (1961). The phosphonates of formula V are either known (cf. J. Org. Chem. *30*, p.

680 (1965)) or may be prepared in a manner analogous to the known methods (for example, J. Amer. Chem. Soc. *88*, p. 5654 (1966).

The compound of formula VII may be obtained by treating the compound of formula VI with a reducing agent. Such a reducing agent is any substance capable of selectively reducing a keto group to a hydroxy group, preferably a complex metal hydride, especially a borohydride, for example sodium borohydride, zinc borohydride or lithium perhydro-9b-boron phenalkyl hydride (J. Amer. Chem. Soc. *92*, p. 709 (1970)), or a complex aluminium hydride, for example sodium-bis-(2-methoxy-ethoxy)-aluminium hydride. The reduction is generally carried out at a temperature of from −10 to 50°C in a solvent which is inert towards the hydride, for example, an ether, for example diethyl ether, dimethoxyethane, dioxan, tetrahydrofuran or diethyleneglycol dimethyl ether; or a hydrocarbon, for example benzene, or in a mixture of an alcohol and water, for example methanol/water.

The isomeric α- and β-hydroxy compounds resulting from this reduction may be separated into the two isomers by the usual chromatographical methods. The subsequent reactions can also be carried out using a mixture of these two isomers, so that a separation into α- and β-hydroxy compounds can be performed at any stage following the reduction.

In the case where R^3 represents the group $COOC_2H_5$, it is possible in the preparation of the compound of formula VIII to split off the protective group by saponification and subsequent decarboxylation, for example by a treatment with an acid or a base in water, an alcohol or an aqueous alcohol. The formyl group may also be eliminated in this manner. The benzyl group is eliminated by a treatment with an acid, for example boron trifluoride etherate in glacial acetic acid, or by catalytic hydrogenation, whereas the tert.-butyl group is split off by means of high temperatures, for example of from 90 to 250°C. The splitting-off reaction may be carried out on any of the compounds of formula IV, VI or VII but advantageously on the compounds of formula VI or VII.

The removal of the protective group from the compound of formula VI yields the pyrrolidone of formula X, which may, however, be obtained more directly from 5-hydroxymethyl-pyrrolidone of formula II. The compound of formula II can be oxidized as described above for the conversion of compound III into compound IV to yield the compound of formula IX, which can also be obtained by splitting off the nitrogen protective group from compound IV and this can be reacted under the conditions of a Horner reaction (see conversion of IV into VI) in the presence of a phosphonate of formula V to yield a compound of formula X. The reduction of the ketocarbonyl group in this compound in the manner described above (conversion of VI into VII) provides the compound of formula VIII.

The alcohol function in the compound of formula VIII can conveniently be protected by any protective group easy to split off, especially by one of those mentioned in the disclosure for the conversion of compound II into compound XIV. For the conversion of a compound of formula VIII into a compound of formula XI, the particularly suitable protective groups are those which are introduced by acid catalysis, predominantly by reaction with an enol ether. As the enol ether, 2,3-dihydropyran, ethyl vinyl ether or methylisopropenyl ether, and as the acid catalyst *p*-toluenesulfonic acid or sulfuric acid are especially suitable. The reaction is advantageously carried out in a solvent, for example diethyl ether, dioxane or benzene, at temperatures of from −10 to +60°C.

The pyrrolidone of formula XI is alkylated by means of a carboxylic acid derivative of formula XII according to the usual methods, by deprotonizing the nitrogen atom by means of a suitable base, for example sodium or potassium hydroxide, sodium or potassium amide, sodium hydride, potassium tert.-butylate, lithium diisopropyl amide or lithium cyclohexyl-iso-propyl amide amide, and then adding the alkylating agent in substance or in solution in the corresponding solvent.

As the substituent Y in the compound of formula XII, the acid radical of methane-sulfonic acid, *p*-bromobenzene-sulfonic acid or *p*-toluene-sulfonic acid is especially suitable as is chlorine, bromine or iodine, bromine and chlorine being of outstanding importance in this connection.

The reaction of a base with the compound of formula XI is carried out with exclusion of air and moisture since the base and the resulting anion are sensitive to air and moisture. As the solvent, there is preferred an aprotic polar liquid which has a sufficient dissolving power at low temperatures and which is inert under the reaction conditions. Where required to reduce the solidification point, there may be used a mixture of two or more solvents preferably ethers, for example, dimethyl ether, diethyl

ether, diisopropyl ether, tetrahydrofuran, dioxane, glycol dimethyl ether, dimethylformamide, dimethylsulfoxide, or toluene.

The reaction temperatures generally range from −30°C to +80°C, preferably from −10 to +50°C, in particular from 0°C to room temperature. The reaction is generally carried out by adding a solution of the pyrrolidone of formula XI with agitation to a frozen solution of the base in one of the said solvents, so as to maintain the temperature range desired for the reaction; the components may also be added to one another vice versa.

The alkenyl derivative of formula XII is then added to the frozen solution thus obtained so that the temperature range of the reaction mixture is not substantially exceeded as a result of the exothermic reaction.

After the addition, the mixture is generally stirred for half an hour to 12 hours and then worked up, for example by adding a determined amount of water to the reaction mixture, separating the organic phase, extracting the aqueous phase several times with an organic solvent, drying the combined organic phases and concentrating them. In a few cases, the residue can be purified by a high-vacuum distillation, in most cases only by column chromatography. In many cases, the products are obtained in such a pure state that purification is unnecessary.

To split off the alcohol protective group R^5 for the conversion of the compound of formula XIII into a compound of formula I or into the corresponding acid, the usual reactants and reaction conditions are used. In the compound of formula XIII, the alcohol function is preferably protected by an acetal group which is split off, in the simplest case, by an acid hydrolysis with dilute aqueous/alcoholic acid, preferably dilute aqueous-alcoholic acid, at 10—50°C, or by heating it with 60—70% acetic acid at 50—60°C to yield the compound of formula I.

Depending on the reaction conditions, either an ester of formula I or the corresponding acid is obtained, which may then, optionally, be converted into a further derivative, for example, a metal or amine salt, ester, or an other ester as appropriate.

The above alkylation reaction for the conversion of the compound of formula XI into the compound of formula XIII may also be carried out using the carboxylic acid corresponding to formula XII (R^2=H), and the resulting compound of formula XIII (R^2=H) may be converted into compounds of formula I (R^2=H) by splitting off the alcohol protective group. In the same manner, the compound of formula VIII may be alkylated as above, optionally using either a carboxylic acid ester derivative of formula XII or a carboxylic acid derivative of formula XII (R^2=H). In this case, the compound of formula I is obtained in a single step.

The second reaction method (b) of the invention also starts from 5-hydroxymethyl-pyrrolidone-(2) of formula II. It starts by introducing the alcohol protective group R^6 to yield a compound of formula XIV.

Suitable protective groups R^6 for the hydroxymethylpyrrolidone, are those groups which can be split off under mild conditions, for example by acid hydrolysis or hydrogenation, in particular the allyl, benzyl, tert.-butyl and chloromethyl groups, as well as enol ether groups (cf. J. Org. Chem. *38*, 3224 (1973); Tetrah. Lett. 107 (1972)).

The alcohol group may alternatively be protected by an acyl group, advantageously by reaction with acetic anhydride in pyridine at −10 to +20°C.

It is however preferred to form an acetal, by reacting the alcohol of formula II with an enol ether, for example 2,3-dihydropyran, ethylvinyl ether or methyl-*iso*-propenyl ether, in an aprotic solvent in the presence of a catalytic amount of a strong acid, for example, a mineral acid, for example hydrochloric acid, sulfuric acid or phosphorus oxy-chloride; a Lewis acid, for example boron trifluoride etherate; or an organic acid, for example, *p*-toluene-sulfonic acid or trifluoroacetic acid.

As the solvent, aliphatic and aromatic hydrocarbons, for example, pentane and benzene; halohydrocarbons, for example, chloroform, and methylene chloride; nitriles, for example acetonitrile; and ethers, for example diethyl ether or dioxane, have proved to be useful. The reaction is preferably carried out at −10 to +60°C for a period of from 1 hour to about 24 hours. To isolate the compound of formula XIV, the reaction mixture is generally shaken with a sufficient amount of an acid binder, preferably a saturated, aqueous sodium bicarbonate solution, or if water is to be excluded, for example triethylamine is added, the organic phase is dried by means of sodium sulfate, and the product is purified, after elimination of the solvent, by high-vacuum distillation or by column chromatography.

The subsequent alkylation reaction is carried out as described for the reaction of the compound of formula XI to yield the compound of formula XIII, the alkylating agent being, however, an allyl halide, preferably allyl chloride or allyl bromide

The olefin of formula XV may be converted into the aldehyde of formula XVI

by ozonolysis as disclosed in the art [cf.-Chem. Rev. 58. p. 990 (1958), Tetrah. Lett., *36*, p. 4273 (1966)], for example, in the following manner:

The olefin is dissolved, optionally with the exclusion of moisture, in a determined amount of methanol, with which a halogeno hydrocarbon, for example methylene chloride, may optionally be admixed. Into this solution, the equivalent amount of ozone is introduced at a temperature of from −100 to −50°C, preferably at −70°C. A slight excess amount of ozone does not influence the yield. Excess ozone is then expelled by an inert gas, dimethyl sulfide is added to reduce the products obtained by the ozonolysis, and stirring is continued for about 1 hour at −10°C, 0°C and 20°C, respectively.

To isolate the aldehyde, the solution is generally concentrated *in vacuo* at the lowest possible temperature, the residue is optionally treated with a saturated sodium bicarbonate solution, and the product is then extracted with an appropriate solvent, preferably benzene, or directly chromatographed.

The aldehyde of formula XVI is used either directly for the subsequent Wittig reaction or after purification, for example by column chromatography.

The compound of formula XIX is obtained by reacting a phosphonium ylide of formula XVII, in which R^7 preferably represents a phenyl group, with the aldehyde of formula XVI in an appropriate solvent. The phosphonium ylides and the phosphonium salts, from which they are derived, may be prepared according to methods analogous to those described in the art [J. Amer. Chem. Soc. *91*, p. 5675 (1969)].

For the preparation of the ylide, there may be used an inorganic base, for example, sodium hydride, sodium amide, lithium amide or potassium tert.-butylate, or an organic base, for example, an alkali metal organic compound, for example lithium butyl or lithium di-isopropyl amide, or the sodium salt of dimethyl sulfoxide.

As the solvent, there may be used an ether, for example, diethyl ether, tetrahydrofuran, or diethylene glycol dimethyl ether; a di-lower alkyl sulfoxide ,for example dimethyl sulfoxide; or an amide of a carboxylic acid, for example dimethylformamide, or di-methyl-acetamide.

The solvent preferred is dimethyl sulfoxide, and as the base, the sodium salt of dimethyl sulfoxide is preferably used. Under these conditions, *cis*-double bonds are preferentially formed.

The preparation of the ylide and the subsequent reaction with the aldehyde may be carried out without isolation of intermediate products, for example in the following manner:

The solution of the phosphonium salt is added at room temperature, with the exclusion of humidity and under an inert gas, to one equivalent of a base which is also dissolved in an aprotic solvent, for example dimethyl sulfoxide. After stirring for about 1 hour, a solution of from 0.30 to 0.95 equivalent of the aldehyde is added. The reaction is complete after 2 to 24 hours. The solution is acidified with a mineral acid at −5° to +5°C, the acid is extracted from the reaction mixture with a suitable solvent, for example an ether, methylene chloride or benzene, the organic phase is dried and concentrated. To separate by-products and the phosphine oxide, the acid is reconverted into the alkali metal salt thereof, and the aqueous phase is extracted with a suitable solvent. From the aqueous phase, the carboxylic acid of formula XIX is isolated by acidification and extraction again with an appropriate solvent.

To separate the triphenyl phosphine oxide and the diphenyl-ω-hydroxy-carbonyl-alkyl-phosphine oxide obtained by hydrolysis of excess ylide, the crude material may be dissolved in ether, preferably diethyl ether, and the phosphine oxides are allowed to crystallize at temperatures below −20°C. Under these conditions, the desired reaction products remain in a dissolved state and are separated together with the solvent from the contaminants.

The esters of formulae XX and XXI may be prepared according to methods analogous to those described in the art. For example, the acid can be esterified with the corresponding alcohol in the presence of a strong acid, for example, sulfuric acid, hydrochloric acid, *p*-toluene-sulfonic acid, trifluoroacetic acid, optionally in the presence of an entrainer for the resulting water, the alcohol being used in excess. Under these conditions, the protective group R^6 is simultaneously split off, and the compound of formula XXI is obtained directly. In contradistinction thereto, esterification with an alcohol in the presence of a carbodiimide does not attack the protective group R^6. The reaction with a diazoalkane, preferably diazomethane, in an inert solvent, leads to the same result as does the reaction of the sodium salt of the acid with an alkyl halide in a polar solvent, for example dimethylformamide.

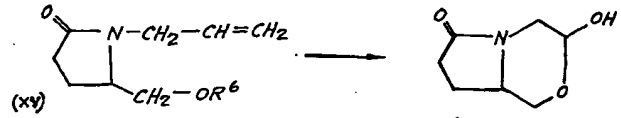
As indicated above, the splitting-off reaction f the protective group R^6 and the esterification can be carried out in a single step. Alternatively, the ester of formula XX

is heated to 50—80°C for about 30 minutes in an alcohol, for example, methanol, ethanol or isopropanol, in the presence of an acid catalyst to split ff the protective group. The compound of formula XXI is then neutralized and isolated by extraction with an appropriate solvent, for example methylene chloride, chloroform or diethyl ether.

When the alcohol protective group is split off from the compound of formula XIX mainly in an aqueous medium in the presence of one of the above acid catalysts, the hydroxy-carboxylic acid of formula XXVI is obtained, which again may either be esterified or used directly for further reaction steps.

The compounds of formula XIX, XX, XXI and XXVI may also be obtained by alkylating the compounds of formulae XIV or II with a carboxylic acid ester derivative of formula XII or a carboxylic acid derivative of formula XII (R^2=H), the alkylation conditions given for the compounds of formula XI being accordingly applied to these reaction steps.

The aldehydes of formula XVI may be cyclisized slowly to give the lactols of the formula XXIV while splitting off the corresponding protective group:



This cyclization reaction may generally be carried out in a solvent, for example, an aliphatic or aromatic hydrocarbon, for example chloroform; in an ether, for example diethyl ether, or dioxane; or in an alcohol, for example methanol or ethanol, with or without an acid catalyst, for example concentrated sulfuric acid, *p*-toluenesulfonic acid or boron trifluoride etherate, at a temperature of from −10° to the boiling point of the solvent used.

The compounds of formulae XXIII and XXIV, respectively, may be obtained directly by alkylating the 5-hydroxymethyl-pyrrolidone-2 of formula II, without introduction of an alcohol protective group R^3, with an allyl halide. The conditions given for the conversion of the compound of formula XI into compounds of formula XIII may also be applied to the introduction of the allyl group into compounds of formula II, the said conditions preferably including the use of potassium hydroxide as a base in dimethyl sulfoxide at a temperature of from +10° to +40°C.

The compound of formula XXII resulting from this reaction can then be subjected to an ozonolysis analogous to that described for the compounds of formula XV to yield the corresponding aldehyde of formula XXIII which, however, has only a poor stability in the open form and has generally already cyclisized during the work-up giving the compound of formula XXIV. This cyclization may optionally be completed by applying the conditions given for the conversion of the compound of formula XVI into the compound of formula XXIV. The compounds of formulae XXIII and/or XXIV can be subjected to a Wittig reaction as described already above for the compounds of formula XVI. This reaction immediately yields the compounds of formulae XXV and XXVI.

The already-mentioned conditions for the reaction sequence including oxidation, Horner reaction, reduction of the ketocarbonyl group for the conversion of the compound of formula II or III into compounds of formula XIII may accordingly be applied to the reaction of the compounds of formula XXI or XXVI yielding the compound of formula I. It does not matter, therefore, if the ester of formula XXI or the free acid of formula XXVI is used or if, at one of the three steps, an acid is esterified or an ester is hydrolyzed to yield the acid. It has, however, proved to be useful to carry out a corresponding conversion reaction into various derivatives only on the final product, unless it is brought about by the reaction conditions applied.

An esterification reaction is carried out according to the methods known in the art, for example described already for the conversion of the compound of formula XIX into a compound of formula XX or XXI.

The reduction of the keto group introduced by the Horner reaction yields a mixture of α- and β-isomers as concerns the resulting secondary hydroxy groups. The separation into the two antipodes may be brought about either in the product resulting from the reduction or in one of the subsequent reaction steps. This means that all the reactions following the reduction of this ketocarbonyl group, for example conversion into the free acid r esterification or conversion into metal or amine salts, can be carried out either on the pure α- and β-isomers and on a mixture of α- and β-isomers.

Unless the separate reaction products are already obtained in a pure state it is advisable to purify them, for example by means of column, thin-layer or high-pressure fluid chromatography.

The compounds of formula I have two asymmetric centres, namely the carbon atom carrying the secondary hydroxy group and the carbon atom neighboring the nitrogen atom in the five-membered ring, which corresponds to the 5-position in the pyrrolidone ring. Since none of the reaction methods indicated provides sterically homogeneous products, the present invention relates to all compounds of formula I, irrespective of the steric arrangement at the various carbon atoms. As well as the two above-mentioned optically isomeric carbon atoms, this also applies to geometrically isomeric compounds with regard to the two double bonds. Generally, it is true to say that the Horner reaction, due to the reaction conditions applied, mainly yields a *trans*-type compound, and the corresponding *cis*-type product, which is obtained to a minor extent only may be eliminated by chromatographic purification steps. Similarly, the Wittig reaction for the introduction of the carboxy side chain yields mainly the corresponding *cis*-olefin. In this case, the *trans*-olefin obtained as a by-product can be separated by corresponding purification operations.

The geometry of the double bonds predetermined in the carboxylic acid derivatives of formula XII is transferred by the alkylation reaction to the final products. This means that, when a *trans*-type derivative of formula XII is used, the final product carries the *trans*-double bond in the carboxy side chain. Accordingly, the same applies to the use of a *cis*-type derivative of formula XII.

Owing to the possibilities of introducing the two double bonds, it can be stated that the geometry of the two double bonds is homogeneous. The mixture of two diasteromers due to the two optically isomeric carbon atoms can be separated, in the case of crystallizable derivatives, into the two racemic diasteromers by fractional crystallization or by means of chromatographic methods, for example column, gaseous-phase or medium- or high-pressure fluid chromatography. The splitting of the racemates into the optically active compounds can be brought about according to the generally used methods, for example, by treatment of the compounds of formula I (R^2=H) with an optically active base, for example brucine.

According to the process of the invention, the following compounds may preferably be prepared in addition to the compounds mentioned in the Examples:

TABLE A

1 - [6 - *n* - butoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - hexyloxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [5 - ethoxycarbonyl - (Z) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [7 - ethoxycarbonyl - (Z) - 2 - hepten - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - hexen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - undecen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E,E,E) - 1,4,6 - octatrien - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1- yl] - 5 - [3 - hydroxy - 4 - methyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 3 - cyclopentyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [2 - hydroxy - 3 - cyclohexyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - ethoxy - (E) - 1 - penten - 1 - yl] - pyrrolidon - 2,
1 - [6 - *n* - hexyloxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [- hydroxy - 6 - methylmercapto - (E) - 1 - hexen - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - isobutyloxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - allylmercapto - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - methylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,

1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - (E) - 1 - buten - 1 -yl] - pyrrolidone - 2,
1 - [5 - methoxycarbonyl - (Z) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - methoxyphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - phenoxyphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy - phenoxy) - 4 - methyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - iso - propoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methyl - phenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - benzyloxy - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyloxy) - (E) - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4,5 - dimethyl - 3 - thienyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [5 - ethoxycarbonyl - (Z) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - fluorobenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylbenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - hexyloxycarbonyl) - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - methoxybenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methyl - benzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 7 - trifluoromethyl - (E) - 1 - hepten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - cyclopentyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [4 - hydroxy - 4 - cycloheptyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenyl) - (E) - 1 buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - butoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - (3,4 - dichlorophenyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - (4 - toluyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyl) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (Z) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4,4 - dimethyl - 5 - (4 - methoxyphenyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - butoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - hexyloxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [5 - ethoxycarbonyl - (E) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [7 - ethoxycarbonyl - (E) - 2 - hepten - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - hexen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E) - 1 - undecen - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - (E,E,E) - 1,4,6 - octatrien - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - methyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 3 - cyclopentyl - (E) - 1 - buten - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 3 - cyclohexyl- (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,

1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - ethoxy - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - hexyloxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 6 - methylmercapto - (E) - 1 - hexen - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - isobutyloxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - allylmercapto - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - methylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - 4 - chlorophenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [5 - methoxycarbonyl - (E) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - methoxyphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - phenoxyphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy - phenoxy) - 4 - methyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - iso - propoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methyl - phenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - benzyloxy - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (5 methyl - 3 - thienyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4,5 dimethyl - 3 - thienyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [5 - ethoxycarbonyl - (E) - 2 - penten - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - fluorobenzyloxy - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylbenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - 6 - *n* - hexyloxy - (E) - 2 - hexen - 1 -yl] - 5 - [3 - hydroxy - 4 (4 - methoxybenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methyl - benzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 7 - trifluoromethoxy - (E) - 1 - hepten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - cyclopentyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - cycloheptyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - ethoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenyl) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2,
1 - [6 - *n* - butoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - (3,4 - dichlorophenyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 5 - (4 - toluyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2,
1 - [6 - methoxycarbonyl - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyl) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2, and
1 - [6 - carboxy - (E) - 2 - hexen - 1 - yl] - 5 - [3 - hydroxy - 4,4 - dimethyl - 5 - (4 - methoxyphenyl) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2.

The compounds of the invention have an activity which is both spasmogenic and spasmolytic, for example they have bronchodilatatory and antihypertensive properties, they are able to inhibit the secretion of gastric juice and they have abortive effects. They may therefore be used as drugs.

The compounds of formula I may be employed in pharmaceutical preparations as free acids, in the form of the physiologically tolerable inorganic or organic salts thereof or as esters of aliphatic, cycloaliphatic or araliphatic alcohols, in admixture or conjunction with a pharmaceutically suitable carrier.

As inorganic salts, there may be used, for example, alkali metal salts, alkaline earth metal salts or ammonium salts; for a formation of salts with organic bases, there may be used bases derived from primary, secondary or tertiary amines which may

contain further hydrophilic groups; for example salts with methyl, triethyl, benzyl, phenylethyl, or allyl amine or also with piperidine, pyrrolidine, morpholine or with ethanolamine, triethanolamine, trimethamine; as esters, there are preferably used esters of lower aliphatic alcohols, such as methyl, ethyl, propyl, butyl, or hexyl esters, and benzyl esters.

The acids, salts or esters may be administered in the form of an aqueous solution or suspension thereof or in a solution or suspension in a pharmaceutically suitable organic solvent, for example, a mono- or polyhydric alcohol, for example ethanol, ethylene glycol or glycerol; an oil, for example sunflower oil or castor oil; an ether, for example diethylene glycol dimethyl ether, or a polyether, for example polyethylene glycol, or even in the presence of pharmaceutically suitable polymer carriers, for example polyvinyl pyrrolidone.

Pharmaceutical preparations are, for example, the usual galenic infusion or injection solutions or suspensions. Orally administrable forms are, for example, dragees, capsules and tablets, and locally administerable compositions, for example, creams, emulsions, suppositories and especially sprays.

The compound ester or salt of the invention is dissolved, if intended for use as a spray, in the usual, physiologically tolerable solvents which do not irritate the taste, for example water or ethanol, or it is suspended for instance in a lower alkyl ester of a higher fatty acid, for example, myristic acid isopropyl ester, optionally with an addition of a surfactant as stabilizer, for example a sorbitan- or pentaerythritol fatty acid ester, and it may be packaged together with the usual inert propellants in an aerosol spray container. The said compositions may, however, also be administered using a conventional spraying device operated by compressed air, or using a flexible container.

The compounds of the invention may further be used in combination with one or more other active ingredients, among which the following compounds may be especially mentioned: Diuretics, for example frusemide, antihyperglycemics, for example glycodiazin, tolbutamide, glibenclamide, phenformin, buformin, metformin, or circulatory agents in the broadest sense of the term, for example cardiovascular-dilatatory agents, such as chromonar or prenylamine, antihypertensive agents, for example, reserpin, α-methyl-dopa or clonidines, or anti-arrhythmic, antihyperlipidemic or geriatric agents, and other compositions acting on the metabolism, psychopharmaceuticals, for example chlorodiazepoxide, diazepam or heprobamate, as well as vitamins, and other prostaglandins or prostaglandin-like compounds and prostaglandin antagonists.

The pharmaceutical preparations may be in unit dosage form, and may comprise from 5 to 5000 mg of the active ingredient per unit dose, preferably from 5 to 500 mg.

For the various indications, the following dosage units and daily dosage units are suggested:

Bronchidilatory effect (as a spray):			
Dosage unit:	0.3 to 3,000 μg	(per spray shot)	
preferable unit:	3 to 600 μg		
daily dosage unit:	0.3 to 30 mg		
Antihypertensive effect:			
Dosage unit:	5 to 5,000 μg		
preferable unit:	5 to 500 μg	parenteral (i.v.)	
daily dosage unit:	5 to 50 mg		
oral administration:			
dosage unit:	1 to 100 mg		
preferable unit:	1 to 50 mg	oral	
daily dosage unit:	10 to 500 mg		

The dosage units administered against gastro-intestinal turbulances correspond to those mentioned for the use as antihypertensive agents.

The compounds of the formulae III, IV, VI, VII, VIII, IX, X, XI, XIII, XIV, XV, XVI, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII and XXVIII are valuable intermediates for the manufacture of the compounds of formula I.

The following Examples 2 and 6 illustrate the invention. Examples 1, 3, 4 and 5 illustrate the preparation of various intermediates.

EXAMPLE 1

Compounds of the general formula VIII

a_1) 1-ethoxycarbonyl-5-hydroxymethyl-pyrrolidone-2 (III)

0.25 Mol of 5-hydroxymethyl-pyrrolidone-2 were dissolved in 150 ml of dried

dimethyl sulfoxide, and 0.3 mol of potassium hydroxide powder was added. While cooling with ice, 0.3 mol of chloroformic acid ethyl ester was added dropwise within 30 minutes. Stirring was continued for 2 hours, whereupon the reaction solution's temperature rose to room temperature. Water was added, and the product was extracted with ether, dried, concentrated and distilled.

Boiling point under a pressure of 0.5 mm Hg: 171—178°C.

b_1) 1-ethoxycarbonyl-5-formyl-pyrrolidone-2 (IV)

0.075 mol of chromium(VI) oxide was added to 0.15 mol of pyridine in 160 ml of methylene chloride, and the mixture was then stirred for 15 minutes at room temperature. It was cooled to 0°C, 0.01 mol of 1-ethoxycarbonyl-5-hydroxymethyl-pyrrolidone-1 as a solution in 40 ml of methylene chloride was added, and stirring was continued for 40 minutes while cooling with ice. 0.3 Mol of sodium bisulfate monohydrate powder was added, and stirring was continued for 30 minutes while cooling with ice. The product was suction-filtered, dried with sodium sulfate, and concentrated *in vacuo* at 5—10°C. The crude 1-ethoxycarbonyl-5-formyl-pyrrolidone-2 could be used without further purification for the next reaction step.

c_1) (VI)

1) 1 - Ethoxycarbonyl - 5 - (3 - oxo - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

0.033 Mol of sodium hydride was added to 0.03 mol of dimethyl-2-oxoheptylphosphonate in 140 ml of absolute dimethoxy-ethane, and the suspension was stirred for 1.5 hours at room temperature. Then, 0.03 mol of 1-ethoxycarbonyl-5-formyl-pyrrolidone-2 as a solution in 10 ml of dimethoxyethane was added, and stirring was continued for 2.5 hours at room temperature. The product was neutralized with glacial acetic acid and concentrated. The residue was chromatographed on silica gel with chloroform/ethyl acetate (4:1) as an eluent.

NMR spectrum at δ=6.0—7.0 ppm (m) CH—*CH*=*CH*—C(=O) 2 prot.

Accordingly, the following compounds were synthesized as above:

2) 1 - Ethoxycarbonyl - 5 - (3 - oxo - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

NMR spectrum: δ=6.0—7.0 ppm (m) CH—*CH*=*CH*—C(=O) 2 prot.

δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.

3) 1 - Ethoxycarbonyl - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

NMR spectrum: δ=0.95 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.3 ppm (s) 2 prot.
δ=3.5 ppm (q) 2 prot.

4) 1 - Ethoxycarbonyl - 5 - [3 - oxo - 4 - (3 - trifluoromethyl - phenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

NMR spectrum: δ=4.7 ppm (s) CH_2—O— 2 prot.
δ=6.9—7.8 ppm (m) aromatic prot. 4 prot.

d_1) (VII)

1) 1 - Ethoxycarbonyl - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

0.2 Mol of anhydrous zinc chloride were suspended in 300 ml of dimethoxyethane, and 0.8 mol of sodium borohydride was added cautiously. The mixture was then stirred for 1 hour at room temperature, filtered, and 0.08 mol of 1-ethoxy-carbonyl-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 in 50 ml of dimethoxyethane was added dropwise within 10 minutes to the so-obtained solution, and stirring was continued for 2.5 hours at room temperature. The solution was acidified with glacial acetic acid, concentrated, and the residue was chromatographed on silica gel with chloroform/methanol (95:5) as the eluent.

NMR: δ=5.3—5.8 ppm (m) *CH*=*CH* 2 prot.

In the same manner, the following compounds were synthesized from the substances mentioned sub c_I 2, 3, 4:

2) 1 - Ethoxycarbonyl - 5 - (3 - hydroxy - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=5.3—5.8 ppm *CH=CH* 2 prot.

3) 1 - Ethoxycarbonyl - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

NMR: =0.93 ppm (s) $C(CH_3)_2$ 6 prot.
=5.2—5.7 ppm (m) *CH=CH* 2 prot.

4) 1 - Ethoxycarbonyl - 5 - [3 - hydroxy - 4 - (3 - trifluoromethyl - phenoxy) - (E) - 1 - buten - 1 - yl)] - pyrrolidone - 2

NMR: =4.65 ppm (s) CH_2—O 2 prot.
=5.25—5.7 ppm (m) *CH=CH* 2 prot.

e_I: (VIII)

1) 5-(3-Hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2

0.05 Mol of 1 - ethoxycarbonyl - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2 were suspended in 100 ml of 0.5 N hydrochloric acid, and the suspension was then heated to 75—80°C for 3 hours. After cooling, the suspension was extracted with ether, dried and concentrated. Chromatography on silica gel with chloroform/methanol (9:1) was indicated for purification purposes.

IR spectrum: 1680 cm^{-1} ν C=O
NMR spectrum: δ=5.3—5.8 ppm (m) *CH=CH* 2 prot.

In an analogous manner, the following compounds were synthesized from the substances cited sub d_I 2, 3, 4:

2) 5-(3-Hydroxy-4,4-dimethyl-(E)-1-octen-1-yl)-pyrrolidone-2

IR: 1680 cm^{-1} ν C=O
NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=5.3—5.8 ppm (m) *CH=CH* 2 prot.

3) 5-(3-Hydroxy-4,4-dimethyl-5-ethoxy-(E)-1-penten-1-yl)-pyrrolidone-2

IR: 1680 cm^{-1} ν C=O
NMR: δ=0.94 ppm (s) $C(CH_3)_2$ 6 prot.
δ=5.25—5.75 ppm (m) *CH=CH* 2 prot.

4) 5 - [3 - Hydroxy - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

IR: 1680 cm^{-1} ν C=O
NMR: δ=4.6 ppm (s) CH_2O 2 prot.
δ=6.9—7.8 ppm (m) aromatic prot. 4 prot.

a_{II}) 5-Formyl-pyrrolidone-2 (IX)

This product was prepared by oxidation of 5-hydroxymethyl-pyrrolidone-2 as described sub (b_I).

The 5-formyl-pyrrolidone-2 thus prepared was used without further purification for the following step.

NMR: δ=9.8 ppm *CHO* 1 prot.

b_{II}): (X)

1) 5-(3-Oxo-(E)-1-octen-1-yl)-pyrrolidone-2

This product was obtained by reacting 5-formyl-pyrrolidone-2 with dimethyl-2-oxo-heptyl-phosphonate according to (c_I).

NMR: δ=6.0—7.0 ppm (m) $CH=CH-\overset{\overset{O}{\|}}{C}$ 2 prot.

2) Accordingly, the same reaction yielded the 5-[3-oxo-4-(3-trifluoromethylphenoxy)-buten-1-yl]-pyrrolidone-2 from 5 - formyl - pyrrolidone - 2 and dimethyl - [2 - oxo - 3 - (3 - trifluoromethylphenoxy) - propyl] - phosphonate according to (c_I).

NMR: δ=4.65 ppm (s) CH_2—O 2 prot.
δ=6.9—7.75 ppm (m) aromatic prot. 4 prot.

b_{II}.) 5-(3-Oxo-(E)-1-octen-1-yl)-pyrrolidone-2 (X)

This product was obtained from 1-ethoxycarbonyl-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 by a reaction according to (e_I).

The spectroscopic data were identical with those of the derivative prepared sub (b_{II}) 1).

c_{II}): (VIII)

1) 5-(3-Hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2

This product was prepared by reducing 5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 according to d_I). In the same manner, there was prepared:

2) 5 - [3 - Hydroxy - 4 - (3 - trifluoromethylphenoxy) - buten - 1 - yl] - pyrrolidone - 2 by reducing the 5-[3-oxo-4-(3-trifluoromethylphenoxy)] - buten-1-yl]-pyrrolidone-2.

The spectrometric data of the two compounds were identical with the compounds prepared according to e_I 1) and e_I 4).

EXAMPLE 2

Compounds of the general formula I

a_I): (XI)

1) 5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl)]-pyrrolidone-2

0.1 Mol of 5-(3-hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2 together with 0.15 mol of dihydropyran and 0.25 mol of p-toluene-sulfonic acid in 150 ml of dioxan were refluxed for 4 hours. The acid was then neutralized by means of triethylamine, and the solvent was eliminated by distillation *in vacuo*.

Chromatography was carried out on silica gel with chloroform/ethyl acetate (4:1) as the eluent.

NMR: δ= 5.3—5.7 ppm (m) $CH=CH$ 2 prot.
δ=~4.3 ppm (m) O—CH—O 1 prot.
IR: 1680 cm^{-1} ν C=O

The tetrahydropyranyl ether protective group was introduced into the alcohols underlying the following compounds in an analogous manner. There were obtained:

2) 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl)] - pyrrolidone - 2

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
IR: 1680 cm^{-1} ν C=O

3) 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2

NMR: δ=0.94 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.3 ppm (s) CH_2—O 2 prot.
δ=3.46 ppm (q) O—CH_2 2 prot.

4) 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

NMR: δ=4.7 ppm (s) CH_2—O 2 prot.
δ=6.9—7.8 ppm (m) aromatic prot. 4 prot.
IR: 1680 cm^{-1} ν C=O

b_I: (XIII)

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

This product was obtained from 5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl]-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester under the conditions mentioned for Example 1 a_I.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=3.7 ppm (s) $COOCH_3$ 3 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

2) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

This product was obtained as in Example 1 a_I from 5-[3-(tetrahydropyran-2-yloxy)-4,4-dimethyl-(E)-1-octen-1-yl]-pyrrolidone-2 and 6 - bromo - (Z) - 4 - hexen - 1 - yl - carboxylic acid ethyl ester.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1740 cm^{-} ν C=O

3) 1 - (6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy)] - 4,4 - dimethyl - 5 - ethoxy) - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2

The product was obtained in a manner analogous to Example 1 a_I from 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl] - pyrrolidone and 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester.

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.7 ppm (s) $COOCH_3$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

4) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydro - pyran - 2 - yloxy) - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

The product was obtained in a manner analogous to Example 1 a_I from 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2 - and 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid ethyl ester.

NMR: δ=5.2—5.7 ppm *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1730 cm^{-1} ν C=O

5) 1 - (6 - Methoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

This product was obtained from 5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl)]-pyrrolidone-2 by alkylation with 6-bromo-(E)-4-hexen-1-yl-carboxylic acid methyl ester according to the conditions mentioned in Example 1 a_I.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=3.7 ppm (s) $COOCH_3$ 3 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

6) 1 - (6 - Ethoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

The product was obtained in a manner analogous to Example 1 a_I from 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2 and 6-bromo-(E)-4-hexen-1-yl-carboxylic acid ethyl ester.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
0.9 ppm (s) $C(CH_3)_2$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

c_I: (I)

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxyl) - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

0.05 Mol of 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl]-pyrrolidone-2 were stirred in 100 ml of 1% methanolic oxalic acid for 4 hours at room temperature and then for 4 hours at 40°C. The acid was neutralized with triethylamine, and the reaction mixture was concentrated. Purification was carried out by chromatography on silica gel using toluene/ethyl acetate/methanol (5:4:0.3).

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=3.7 ppm (s) $COOCH_3$ 3 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

The following compounds were prepared from the corresponding tetrahydropyranyl ethers in the manner described above:

2) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1740 cm^{-1} ν C=O

3) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.7 ppm (s) $COOCH_3$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

4) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

NMR: δ=5.2—5.7 ppm *CH=CH* 4 prot.
1680 cm^{-1} ν C=O
1730 cm^{-1} ν C=O

5) 1 - (6 - Methoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=3.7 ppm (s) $COOCH_3$ 3 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

6) 1 - (6 - Ethoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.

a_{II}) 1 - (6 - Methoxycarbonyl - (Z) - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained by alkylating 5-(3-hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2 with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester in a manner analogous to Example 1 a_I.

The spectroscopical data were identical with those of the compound obtained according to Example 2 c_I.

a_{III}: (XIII, R^2=H)

1) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octen - 1 - yl)] - pyrrolidone - 2

This product was obtained from 5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl]-

pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid according to the conditions mentioned in Example 1 a_I.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1705 cm^{-1} ν C=O

2) 1 - (6 - carboxy - (E) - 2 - hexen - 1 - yl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

This product was prepared from 5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl]-pyrrolidone-2 by alkylation with 6-bromo-(E)-4-hexen-1-yl-carboxylic acid according to the conditions indicated in Example 1 a_I.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1705 cm^{-1} ν C=O

b_{III}: (I, R^2=H)

1) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was prepared from 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-[3-(tetrahydropyran-2-yloxy)-(E)-octen-1-yl]-pyrrolidone-2 in a manner analogous to Example 2 c_I but using a mixture of 100 ml of ethanol and 50 ml of 6% aqueous oxalic acid as a reaction medium instead of methanol.

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1705 cm^{-1} ν C=O

2) 1 - (6 - Carboxy - (E) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - (E) - 1 - octen - 1 - yl] - pyrrolidone - 2

This product was prepared from 1-(6-carboxy-(E)-2-hexen-1-yl)-5-[3-(tetrahydropyran-2-yloxy)-(E)-1-octen-1-yl]-pyrrolidone-2 in a manner analogous to the above conditions.

NMR: δ=5.3—5.8 ppm (n) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1700 cm^{-1} ν C=O

a_{IV}) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2 (I, R^2=H)

This product was obtained in a manner analogous to Example I a_I from 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2 and 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid.

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
IR: 1680 cm^{-1} ν C=O
1700 cm^{-1} ν C=O

a_V) (I)

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

0.03 Mol of 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-(3-hydroxy(E)-1-octen-1-yl)-pyrrolidone-2 was dissolved in 75 ml of diethyl ether, and an ethereal diazomethane solution was added until the yellow colour remained unchanged. Excess diazomethane was destroyed by means of a trace of glacial acetic acid. The solution was concentrated, and after elimination of all the solvents, the pure end product was obtained.

The physical data were the same as in Example 2 c_I 1).

2) 1 - (6 - *iso* - propoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl)] - pyrrolidone - 2

0.02 Mol of 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-(3-hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2 were dissolved in 40 ml of a 0.5-molar aqueous sodium hydroxide solution, and the solution was stirred for 14 hours at room temperature. It was then concentrated and the remaining traces of water were eliminated under greatly reduced pressure.

The remaining residue was dissolved in 75 ml of dimethylformamide, and 0.025 mol of *iso*propyl iodide was added. Stirring was continued for 7 hours at room temperature, ether and water were added, the aqueous phases was extracted with ether several times, the organic phases were united, dried and concentrated. Purification was made by chromatography on silica gel and elution with toluene/ethyl actetate/*iso*propanol (5:4:0.5).

NMR: δ=5.3—5.8 ppm (m) *CH=CH* 4 prot.
δ=1.2 ppm (d) $CH(CH_3)_2$
IR: 1680 cm^{-1} ν C=O
1730 cm^{-1} ν C=O

a_{VI} 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2 (I, R^2=H)

30 Milliliters of a 0.5-molar aqueous sodium hydroxide solution were added to 0.01 mol of 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2, and the mixture was stirred overnight at room temperature. It was acidified with dilute hydrochloric acid, and the aqueous phase was extracted several times with ether. The residue resulting after drying and concentration of the solvent could be purified as usual by chromatography.

The physical data were the same as in Example 2 b_{III} 1).

EXAMPLE 3

Compounds of the general formula XIX

a_I) 5-Tetrahydropyran-2-yloxy-methyl-pyrrolidone-2 (XIV)

This product was obtained from 5-hydroxymethyl-pyrrolidone-2 and dihydropyran analogous to Example 2 a_I. Purification was made by chromatography on silica gel with toluene/ethyl acetate/methanol (5:4:1) as an eluent.

NMR spectrum: δ=6.5 ppm (broad single peak) NH 1 prot.
δ=4.6 ppm (broadened single peak) O—*CH*—O 1 prot.

b_I) 1-Allyl-5-(tetrahydropyran-2-yloxy-methyl)-pyrrolidone-2 (XV)

This product was obtained from 5-(tetrahydropyran-2-yloxy-methyl)-pyrrolidone-2 by alkylation with allyl bromide according to Example 1 a_I. Chromatography on silica gel. Eluent: chloroform/acetone (8:2).

NMR spectrum: δ=5.0—6.2 ppm (several multiple peaks) $CH=CH_2$ 3 prot.
δ=4.7 ppm (broadened single peak) O—*CH*—O 1 prot.
IR spectrum: 1680 cm^{-1} ν C=O

c_I) 1-Formylmethyl-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 (XVI)

0.02 Mol of 1-allyl-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 was dissolved in 100 ml of methylene chloride, and 10 ml of methanol were added. The solution was cooled to −78°C, and at this temperature, ozone was passed in until the blue color of the solution did no longer change. The reaction mixture was heated to −20°C. At this temperature, 0.2 mol of dimethyl sulfide was added dropwise. The cooling bath was then removed, and the reaction mixture was stored for 2 hours at room temperature, concentrated and then chromatographed on silica gel using chloroform/acetone (8:2) as the eluent.

NMR: δ=9.6 ppm (s) *CHO* 1 prot.
δ=4.6 ppm (broadened single peak)

d_I) (XIX)

1) 1 - (5 - carboxy - (Z) - 2 - penten - 1 - yl) - 5 - (tetrahydropyran - 2 - yloxy - methyl) - pyrrolidone - 2

0.1 mol of sodium hydride was stirred in 45 ml of dimethyl sulfoxide at 60°C until the evolution of hydrogen ceased. The mixture was then cooled to room temperature and a solution of 0.05 mol of 3-carboxy-butyl-triphenyl phosphonium bromide in 40 ml of dimethyl sulfoxide was added. Stirring was continued for 30 minutes at room temperature. Then, a solution of 0.02 mol of 1-formylmethyl-5-(tetrahydropyran-2-yloxy-methyl)-pyrrolidone in 25 ml of dimethyl sulfoxide was added, and the mixture was heated to 50°C. At this temperature, stirring was continued for 3 hours. After cooling t 10°C, 400 ml of water were added, and the pH was adjusted to 2 by means

of a 5% aqueous sodium bisulfate solution. The solution was once more extracted with ether, dried and concentrated. The residue was purified by chromatography on silica gel, the eluent being chloroform/methanol (95:5).

NMR: δ=9.0 ppm (broad signal) COO*H* 1 prot.
δ=5.2—5.7 ppm (m) *CH=CH* 2 prot.
δ=4.62 ppm (broadened single peak) O—*CH*—O 1 prot.

2) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (tetrahydropyran - 2 - yl-oxymethyl) - pyrrolidone - 2

The reaction was carried out in the above manner from 1 - formylmethyl - 5 - (tetrahydropyran - 2 - yloxymethyl) - pyrrolidone - 2 and 4-carboxy-butyl-triphenyl phosphonium bromide. Chromatography on silica gel. Eluent: chloroform/methanol (95:5).

NMR: δ=9.1 ppm (broad signal) COO*H* 1 prot.
δ=5.2—5.7 ppm (m) *CH=CH* 2 prot.
δ=4.64 ppm (4.64 ppm (broadened single peak) O—*CH*—O 1 prot.

3 1 - (7 - Carboxy - (Z) - 2 - hepten - 1 - yl) - 5 - (tetrahydropyran - 2 - yl - oxymethyl) - pyrrolidone - 2

This product was prepared from 1-formyl-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 and 5-carboxy-pentyltriphenyl-phosphonium bromide in the above manner. Chromatography on silica gel, the solvent being chloroform/methanol (95:5).

NMR: δ=9.0 ppm (broad signal) COO*H* 1 prot.
δ=5.1—5.8 ppm (m) *CH=CH* 2 prot.
δ=4.60 ppm (s) —O—*CH*—O 1 prot.
IR: 1680 cm^{-1} ν C=O
1700 cm^{-1} ν C=O

a_{II}) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (tetrahydropyran - 2 - yloxy - methyl) - pyrrolidone - 2

This product was obtained from 5-(tetrahydropyran-2-yloxy-methyl)-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid according to the method of Example 1 a_I.

Physical data see above.

EXAMPLE 4

Compounds of the general formula XX

a_I) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (tetrahydropyran - 2 - yloxymethyl) - pyrrolidone - 2 (XX)

This product was obtained by esterifying 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 with diazomethane according to Example 2 a_V 1). Chromatography on silica gel, the solvent being carbon tetrachloride/acetone (7:3).

NMR: δ=5.15—5.70 ppm (m) *CH=CH* 2 prot.
δ=4.7 ppm (broad single peak) O—*CH*—O 1 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

a_{II}) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (tetrahydropyran - 2 - yloxymethyl) - pyrrolidone - 2 (XX)

This product was obtained from 5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester according to Example 1 a_I.

The physical data were the same as indicated above.

EXAMPLE 5

Compounds of the general formula XXI

a_I) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - hydroxy - methyl - pyrrolidone - 2 (XXI)

0.01 Mol of 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-tetrahydropyran-2-yloxy-methyl)-pyrrolidone-2 was dissolved in 50 ml of methanol, and the solution was refluxed together with a few grains of p-toluene-sulfonic acid for 3 hours. A drop of

triethylamine was added to neutralise the acid, the solution was concentrated and chromatographed on silica gel using toluene/ethyl acetate/methanol (5:4:1).

NMR: δ=5.2—5.8 ppm (m) $CH=CH$ 2 prot.
δ=4.1 ppm ABX-spectrum CH_2—OH
δ=3.7 ppm (s) $COOCH_3$
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

a_{II}) (XXI)

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - hydroxymethyl - pyrrolidone - 2

1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (tetrahydropyran - 2 - yloxy - methyl) - pyrrolidone was treated in methanol with *p*-toluene-sulfonic acid as indicated in Example 5 a_I. Chromatography and physical data were the same as indicated above.

2) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - hydroxymethyl - pyrrolidone - 2

This product was prepared as above (a_{II} 1)) using ethanol instead of methanol. Chromatography on silica gel using toluene/ethyl acetate/ethanol (5:4:1.5).

NMR: δ=5.2—5.8 ppm (m) $CH=CH$ 2 prot.
IR: 1680 cm^{-1} ν C=O
1730 cm^{-1} ν C=O

3) 1 - (7 - Ethoxycarbonyl - (Z) - 2 - hepten - 1 - yl) - 5 - hydroxymethyl - pyrrolidone - 2

This product was obtained from 1-(7-carboxy-(Z)-2-hepten-1-yl)-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 by a treatment with ethanol in the presence of p-toluenesulfonic acid as indicated above (a_{II}) 1)). Chromatography on silica gel using toluene/ethyl acetate/ethanol (5:4:1.5) as the eluent.

NMR: δ=5.2—5.85 ppm (m) $CH=CH$ 2 prot.
δ=1.35 ppm (Z) O—CH_2—CH_3 3 prot.
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

a_{III}) (XXI)

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - hydroxymethyl - pyrrolidone - 2

This product was obtained from 5-hydroxymethyl-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester as in Example 1 (a_I). Purification and physical data as above.

2) 1-(6-Methoxycarbonyl-(E)-2-hexen-1-yl)-hydroxy-methyl-pyrrolidone-2

This product was prepared from 5-hydroxymethyl-pyrrolidone-2 by alkylation with 6-bromo-(E)-4-hexen-1-yl-carboxylic acid methyl ester according to Example 1 a_I. Chromatography on silica gel, the solvent being toluene/ethyl acetate/methanol (5:4:1).

NMR: δ=5.2—5.9 ppm (m) $CH=CH$ 2 prot.
δ=3.65 ppm (s) $COOCH_3$
IR: 1738 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

a_{IV}) 1-Allyl-5-hydroxymethyl-pyrrolidone-2 (XXII)

This product was obtained by alkylation of 5-hydroxymethyl-pyrrolidone-2 with allyl bromide according to Example 1 a_I. Boiling point under a pressure of 0.3 mm Hg: 161—169°C.

NMR spectrum: δ=5.0—6.3 ppm (several multiple peaks) $CH=CH_2$ 3 prot.
IR spectrum: 1680 cm^{-1} ν C=O

b_{IV}) 1-Formylmethyl-5-hydroxymethyl-pyrrolidone-2-δ-lactol (XXIV)

This product was obtained by ozonolysis of 1-allyl-5-hydroxy-methyl-pyrrolidone-

2 according to Example 3 c_I. After concentration of the reaction mixture, the crystallized residue was recrystallized from ethanol.

M.p. 152—154°C.

c_{IV}) (XXVI)

1) 1-(5-Carboxy-(Z)-2-penten-1-yl)-5-hydroxy-methyl-pyrrolidone-2

This product was obtained from 1-formylmethyl-5-hydroxymethyl-pyrrolidone-2-δ-lactol and 3-carboxy-propyl-triphenyl phosphonium bromide as in Example 3 d_I. Chromatography was performed on silica gel using chloroform/methanol (8:2) as the solvent.

NMR: δ=5.15—5.85 ppm (m) *CH=CH* 2 prot.
IR: 1680 cm^{-1} ν C=O
1703 cm^{-1} ν C=O

2) 1-(6-Carboxy-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2

This product was obtained from 1-formylmethyl-5-hydroxymethyl-pyrrolidone-2-δ-lactol and 4-carboxy-butyl-triphenyl phosphonium bromide according to Example 3 d_I. Chromatography on silica gel, eluent: chloroform/methanol (85:15).

NMR: δ=5.2—5.8 ppm (m) *CH=CH* 2 prot.
IR: 1700 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

$c_{IV'}$) 1-(6-Carboxy-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2

This product was obtained from 5-hydroxymethyl-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid according to Example 1 a_I. Physical data as above.

$c_{IV''}$) 1-(5-Carboxy-(Z)-2-penten-1-yl)-5-hydroxymethyl-pyrrolidone-2

This product was obtained from 1-(5-carboxy-(Z)-2-penten-1-yl)-5-(tetrahydropyran-2-yloxymethyl)-pyrrolidone-2 by splitting off the tetrahydropyranyl protective group according to Example 2 b_{III}. Physical data as above.

d_{IV}) 1-(6-Methoxycarbonyl-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2

This product was obtained by esterifying 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2 with methanol. The reaction was analogous to Example 5 a_{II}. The physical data corresponded to those of the compound obtained in Example 5 a_I.

EXAMPLE 6

Compounds of the general formula I

a_I: (XXVII)

1) 1-(6-Methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2

This product was obtained by oxidation of 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

2) 1-(6-Ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2

This product was prepared by oxidation of 1-(ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

3) 1-(6-Methoxycarbonyl-(E)-2-hexen-1-yl)-5-formyl-pyrrolidone-2

This product was prepared by oxidation of 1-(6-methoxycarbonyl-(E)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

4) 1-(7-Ethoxycarbonyl-(Z)-2-hepten-1-yl)-5-formyl-pyrrolidone-2

This product was obtained by oxidation of 1-(7-ethoxycarbonyl-(Z)-2-hepten-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

Owing to their instability, the so-obtained compounds of formula XXVII 1 to 4 were used without further purification as crude products for the next step.

b_I: (XXVIII)

According to the method indicated in Example 1 c_I, the following compounds were prepared:

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was prepared from 1-(6-methoxycarbonyl)-(Z)-2-hexen-1-yl-5-formyl-pyrrolidone-2 and dimethyl-2-oxo-heptyl-phosphonate. Chromatography: toluene/ethyl acetate/methanol (5:4:0.3).

NMR: δ=5.2—5.8 ppm (m) *CH*=*CH* (cis) 2 prot.
δ=6.05—7.0 ppm (m) *CH*=*CH* (trans) 2 prot.
δ=3.7 ppm (s) $COOCH_3$

2) 1 - (6 - Methoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

The product was prepared from 1-(6-methoxycarbonyl-(E)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-2-oxo-heptyl-phosphonate. Chromatography: toluene/ethyl acetate/methanol (5:4:0.3).

NMR: δ=5.1—5.9 ppm (m) *CH*=*CH* (trans, unconjugated) 2 prot.
δ=6.0—6.9 ppm (m) *CH*=*CH* (trans, conjugated)
δ=3.75 ppm (s) $COOCH_3$

3) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - (E) - 1 - decen - 1 - yl) - pyrrolidone - 2

This product was prepared from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-2-oxo-nonyl-1-phosphonate. Chromatography: toluene/ethyl acetate/methanol (5:4:0.1).

NMR: δ=5.2—5.85 ppm (m) *CH*=*CH* (cis) 2 prot.
δ=6.0—6.7 ppm (m) *CH*=*CH* (trans) 2 prot.
δ=3.75 ppm (s) $COOCH_3$

4) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 5 - ethoxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was prepared from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-(2-oxo-4-ethoxy-3,3-dimethyl-butyl)-phosphonate. Chromatography: toluene/ethyl acetate (5:4).

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.7 ppm (s) $COOCH_3$
δ=5.2—5.8 ppm (m) *CH*=*CH* (cis) 2 prot.

5) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 5 - allyloxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was prepared from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-(2-oxo-4-allyloxy-3,3-dimethyl-butyl)-phosphonate. Chromatography: toluene/ethyl acetate (5:4).

NMR δ=5.0—7.0 ppm (m) all the olefinic protons 6 prot.
δ=3.65 ppm (s) $COOCH_3$

6) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 dimethyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2.

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl - [2 - oxo - 3 - (4 - chlorophenoxy) - phenoxy - 3,3 - dimethyl - propyl] - phosphonate. Chromatography: chloroform/ethyl acetate (4:1)

NMR: δ=1.05 ppm (s) $C(CH_3)_2$ 6 prot.
δ=6.9—7.9 ppm (m) aromatic protons 8 prot.
δ=3.7 ppm (s) $COOCH_3$

7) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (3 - thienyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-[2-oxo-3-(3-thienyloxy)-propyl]-phosphonate. Chromatography: carbon tetrachloride/acetone (7:3)

NMR: δ=5.2—5.9 ppm (m) *CH*=*CH* cis 2 prot.
δ=6.0—6.9 ppm (m) *CH*=*CH* trans 2 prot.
δ=3.7 ppm (s) $COOCH_3$

8) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 6 - pentafluoro - ethyl - (E) - 1 - hexen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-2-(oxo-5-pentafluoroethyl-pentyl)-phosphonate. Chromatography: toluene/ethyl acetate/methanol (5:4:0.5).

NMR: δ=3.7 ppm (s) $COOCH_3$
δ=5.2—5.9 ppm (m) $CH=CH$ cis — 2 prot.
δ=6.0—6.7 ppm (ABX-Spectr.) $CH=CH$ trans — 2 prot.

9) 1 - (6 - Methoxycarbonyl - (Z) - hexen - 1 - yl) - 5 - (3 - oxo - 5 - cyclopentyl - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2.

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl - 2 - (oxo - 4 - cyclopentyl - 3,3 - dimethyl - butyl) - phosphonate. Chromatography: toluene/ethyl acetate (5:4)

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ — 6 prot.
δ=3.7 ppm (s) $COOCH_3$
δ=6.0—7.0 ppm (m) $CH=CH$ trans — 2 prot.

10) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 5 - phenyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-2-oxo-4-phenylbutyl)-phosphonate. Chromatography: carbon tetrachloride/acetone (7:3)

NMR: δ=7.3 ppm (s) aromatic protons — 5 prot.
δ=3.7 ppm (s) $COOCH_3$
δ=5.15—5.75 ppm (m) $CH=CH$ (cis) — 2 prot.

11. 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 5 - (4 - methyl - 2 - chlorophenyl) - 4,4 - dimethyl - (E) - 1 - penten - 1 -yl)] - pyrrolidone - 1

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone and dimethyl - [2 - oxo - 4 - (4 - methyl - 2 - chlorophenyl) - 3,3 - dimethylbutyl] - phosphonate. Chromatography: toluene/ethyl acetate (5:4)

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ — 6 prot.
δ=2.3 ppm (s) CH_3 — 3 prot.
δ=6.1—6.9 ppm (m) $CH=CH$ (trans) — 2 prot.

12. 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 7 - methyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-(2-oxo-6-methyl-heptyl)-phosphonate. Chromatography: chloroform/ethyl acetate (4:1)

NMR: δ=1.05 ppm (d) $CH(CH_3)_2$ — 6 prot.
δ=1.3 ppm (t) $COOCH_2CH_3$ — 3 prot.
δ=5.2—5.9 ppm (m) $CH=CH$ (cis) — 2 prot.

13. 1 - (6 - Ethoxycarbonyl) - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl)-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-(2-oxo-3,3-dimethyl-heptyl)-phosphonate. Chromatography: toluene/ethyl acetate/ethanol (5:4:0.3)

NMR: δ=0.95 ppm (s) $C(CH_3)_2$ — 6 prot.
δ=1.25 ppm (t) $COOCH_2CH_3$ — 3 prot.
δ=5.15—5.95 ppm (m) $CH=CH$ (cis) — 2 prot.
δ=6.0—7.05 ppm (m) $CH=CH$ (trans) — 2 prot.

14) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was prepared from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-

formyl-pyrrolidone-2 and dimethyl - [2 - oxo - 3 - (3 - trifluoromethyl - phenoxy) - propyl] - phosphonate.

Chromatography: toluene/ethyl acetate (5:4)

NMR:	δ=1.2 ppm (t) $COOCH_2CH_3$	3 protons
	δ=4.6 ppm (s) CH_2—O	2 protons
	δ=6.0—6.95 ppm (m) CH=CH	2 protons

15) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (4 - chlorobenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl - [2 - oxo - 3 - (4 - chlorobenzyloxy) - propyl)] - phosphonate.

Chromatography: carbon tetrachloride/acetone (7:3)

NMR:	δ=4.4 ppm and 4.6 ppm (2 Sing.) CH_2—O	4 prot.
	δ=1.2 ppm (t) $COOCH_2$—CH_3	3 prot.
	δ=7.0—7.5 ppm (m) aromatic protons	4 prot.

16) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (2 - thienyl) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-[2-oxo-3-(2-thienyl)-propyl]-phosphonate.

Chromatographie: toluene/ethyl acetate/ethanol (5:4:0.1)

NMR:	δ=3.9 ppm (s) —CH_2	2 prot.
	δ=7.1—7.3 ppm (m) thiophenone protons	3 prot.
	δ=6.0—6.90 ppm (m) CH=CH (trans)	2 prot.

17) 1 - (7 - Ethoxycarbonyl - (Z) - 2 - hepten - 1 - yl) - 5 - (3 - oxo - 5 - ethoxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(7-ethoxycarbonyl-(Z)-2-hepten-1-yl)-5-formyl-pyrrolidone-2 and dimethyl - (2 - oxo - 4 - ethoxy - 3,3 - dimethyl - butyl) - phosphonate.

Chromatography: toluene/ethyl acetate (5:4)

	δ=1.0 ppm (s) $C(CH_3)_2$	6 prot.
	δ=1.2 ppm (t) $COOCH_2CH_3$	3 prot.
	δ=6.0—6.95 (m) CH=CH (trans)	2 prot.

b_I, 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2 (XXVIII)

This product was obtained by alkylation of 5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 and 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid methyl ester according to the method of Example 1 a_I. Physical data and chromatography as in Example 6 b_I 1).

c_I: (I)

The reduction of the above-mentioned α,β-unsaturated ketones of formula XXVIII was carried out as in Example 1 d_I to yield the compounds of formula I. Specifically, the following compounds were prepared:

1) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl - 5 - (3 - hydroxy - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2. Physical data and chromatography as in Example 2 c_I 1).

2) 1 - (6 - Methoxycarbonyl - (E) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(E)-2-hexen-1-yl)-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2. Physical data as in Example 2 c_I 5).

3) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 1 - decen - 1 - yl] - pyrrolidone - 2.

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-(E)-1-decen-1-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/methanol (5:4:0.5)

NMR: δ=5.2—5.85 ppm (m) *CH=CH* 4 prot.
δ=3.75 ppm (s) $COOCH_3$
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

4) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 5 - ethoxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-5-ethoxy-4,4-dimethyl-(E)-1-penten-1-yl)-pyrrolidone-2.

Physical data and chromatography as in Example 2 c_I 3).

5) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 5 - allyloxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-5-allyloxy-4,4-dimethyl-(E)-1-penten-1-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/methanol (5:4:1)

NMR: δ=5.0—6.5 ppm (m) all the olefinic protons 6 prot.
δ=3.65 ppm (s) $COOCH_3$
IR: 1680 cm^{-1} ν C=O
1735 cm^{-1} ν C=O

6) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 - dimethyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1 - (6 - methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - oxo - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 - dimethyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2.

Chromatography: chloroform/ethyl acetate (4:1)

NMR: δ=1.05 ppm (s) $C(CH_3)_2$ 6 prot.
δ=6.9—7.9 ppm (m) aromatic protons 8 prot.
δ=3.7 ppm (s) $COOCH_3$
IR: 1680 cm^{-1} ν C=O
1733 cm^{-1} ν C=O

7) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (3 - thienyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-oxo-4-(3-thienyloxy)-(E)-buten-1-yl]-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/ethanol (6:4:0.2)

NMR: δ=5.3—5.6 ppm (m) *CH=CH* 4 prot.
δ=3.7 ppm (s) $COOCH_3$
IR: 1680 cm^{-1} ν C=O
1738 cm^{-1} ν C=O

8) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 6 - pentafluoroethyl - (E) - 1 - hexen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-6-pentafluoroethyl-(E)-1-hexen-1-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/methanol (5:4:0.5)

NMR: δ=3.7 ppm (s) $COOCH_3$
δ=5.2—5.6 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1730 cm^{-1} ν C=O

9) 1 - (6 - Methoxycarbonyl - (Z) - hexen - 1 - yl) - 5 - (3 - hydroxy - 5 - cyclopentyl - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-hexen-1-yl)-5-(3-oxo-5-cyclopentyl-4,4-dimethyl-(E)-1-penten-1-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/methanol (5:4:0.3)

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=3.7 ppm (s) $COOCH_3$
δ=5.3—5.5 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1740 cm^{-1} ν C=O

10) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 5 - phenyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-5-phenyl-(E)-1-penten-1-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/methanol (5:4:0.1)

NMR: δ=7.3 ppm (s) aromatic protons 5 protons
δ=3.7 ppm (s) $COOCH_3$
δ=5.15—5.50 ppm (m) *CH=CH* 4 protons
IR: 1730 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

11) 1 - (6 - Methoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 5 - (4 - methyl - 2 - chlorophenyl) - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-oxo-5-(4-methyl-2-chlorophenyl)-4,4-dimethyl-(E)-1-penten-1-yl]-pyrrolidone-2.

Chromatography: toluene/ethyl acetate (5:4)

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ 6 prot.
δ=2.3 ppm (s) CH_3 3 prot.
δ=5.3—5.7 ppm *CH=CH* 4 prot.
IR: 1740 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

12) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 7 - methyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-7-methyl-(E)-1-octen-1-yl)-pyrrolidone-2.

Chromatography: chloroform/ethyl acetate/ethanol (8:2:0.5)

NMR: δ=1.0 ppm (d) $CH(CH_3)_2$ 6 protons
δ=1.25 ppm (Z) $COOCH_2CH_3$ 3 protons
δ=5.2—5.5 ppm (m) *CH=CH* 4 protons
IR: 1730 cm^{-1} ν C=O
1675 cm^{-1} ν C=O

13) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-oxo-4,4-dimethyl-(E)-1-octen-1-yl)-pyrrolidone-2.

Physical data as in Example 2 c_I 2).

14) 1 - (Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (3 - trifluoromethyl - phenoxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2.

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-oxo-4-(3-trifluoromethylphenoxy)-(E)-1-buten-1-yl]-pyrrolidone-2.

Physical data as in Example 2 c_I 4).

15) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl - 5 - [3 - hydroxy - 4 - (4 - chlorobenzyloxy) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-oxo-4-(4-chlorobenzyloxy)-(E)-1-buten-1-yl]-pyrrolidone-2.

Chromatography: carbon tetrachloride/acetone (7:3)

NMR: δ=5.1—5.4 ppm (m) *CH=CH* 4 prot.
δ=1.1 ppm (t) $COOCH_2—CH_3$ 3 prot.
δ=7.0—7.5 ppm (m) aromatic protons 4 prot.
IR: 1735 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

16) 1 - (6 - Ethoxycarbonyl - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (2 - thienyl) - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-ethoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-oxo-4-(2-thienyl)-(E)-1-buten-1-yl]-pyrrolidone-2.

Chromatography: toluene/ethyl acetate/ethanol (5:4:0.5)

NMR: δ=7.1—7.3 ppm (m) thiophenone protons 3 prot.
δ=5.2—5.6 ppm (m) *CH=CH* 2 prot.
IR: 1740 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

17) 1 - (7 - Ethoxycarbonyl - (Z) - 2 - hepten - 1 - yl) - 5 - (3 - hydroxy - 5 - ethoxy - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(7-ethoxycarbonyl-(Z)-2-hepten-1-yl)-5-(3-oxo-5-ethoxy-4,4-dimethyl-(E)-1-penten-yl)-pyrrolidone-2.

Chromatography: toluene/ethyl acetatae/ethanol (5:4:0.5)

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=1.2 ppm (t) $COOCH_2CH_3$ 3 prot.
δ=5.15—5.5 ppm (m) *CH=CH* 4 prot.
IR: 1738 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

a_{II}: (XXVII, R^2=H)

1) 1-(5-Carboxy-(Z)-2-penten-1-yl)-5-formyl-pyrrolidone-2

This product was prepared by oxidation of 1-(5-carboxy-(Z)-2-penten-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

2) 1-(6-Carboxy-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2

This product was prepared by oxidation of 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-hydroxymethyl-pyrrolidone-2 according to Example 1 b_I.

The two aldehydes thus prepared were used without further purification as crude products for the following step.

b_{II}: (XXVIII, R^2=H)

1) 1 - (5 - Carboxy - (Z) - 2 - penten - 1 - yl) - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(5-carboxy-(Z)-2-penten-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-(2-oxo-3,3-dimethyl-4-ethoxy-butyl)-phosphonate according to Example 1 c_I.

Chromatography: ethyl acetate/glacial acetic acid (98:2)

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ 6 prot.
δ=5.2—5.5 ppm (m) *CH=CH* cis 2 prot.
δ=6.1—6.9 ppm (m) *CH=CH* trans 2 prot.

2) 1-(6-Carboxy-(Z)-2-hexen-1-yl)-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2

This product was obtained from 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-formyl-pyrrolidone-2 and dimethyl-2-oxo-heptylphosphonate according to Example 1 c_I.

Chromatography: ethyl acetate/glacial acetic acid (98:2)

NMR: δ=5.2—5.85 ppm (m) *CH=CH* (cis) 2 prot.
δ=6.0—6.95 ppm (m) *CH=CH* (trans) 2 prot.

$b_{II'}$: 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - oxo - (E) - 1 - octen - 1 - yl) - pyrrolidone - 2 (XXVIII, R^2=H)

This product was obtained from 5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 by alkylation with 6-bromo-(Z)-4-hexen-1-yl-carboxylic acid according to Example 1 a_I.

Physical data and purification as above.

c_{II}: (I, R^2=H)

1) 1 - (5 - Carboxy - (Z) - 2 - penten - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - penten - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(5-carboxy-(Z)-2-penten-1-yl)-5-(3-oxo-4,4-dimethyl-5-ethoxy-(E)-1-penten-1-yl)-pyrrolidone-2 according to Example 1 d_I.

Chromatography: ethyl acetate/glacial acetic acid (98:2)

NMR: δ=1.0 ppm (s) $C(CH_3)_2$ 6 prot.
δ=5.2—5.5 ppm (m) *CH=CH* 4 prot.
IR: 1705 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

2) 1-(6-Carboxy-(Z)-2-hexen-1-yl)-5-(3-hydroxy-(E)-1-octen-1-yl)-pyrrolidone-2

This product was obtained from 1-(6-carboxy-(Z)-2-hexen-1-yl)-5-(3-oxo-(E)-1-octen-1-yl)-pyrrolidone-2 according to Example 1 d_I.
Chromatography: ethyl acetate/glacial acetic acid (97.5:2.5)

NMR: δ=5.3—5.7 ppm (m) *CH=CH* 4 prot.
IR: 1700 cm^{-1} ν C=O
1682 cm^{-1} ν C=O

a_{III}: (I, R^2=H)

1) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - (E) - 1 - decen - 1 - yl) - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-hydroxy-(E)-1-decen-1-yl)-pyrrolidone-2 according to Example 2 a_{VI}.
Chromatography: ethyl acetate/glacial acetic acid (98:2)

NMR: δ=5.2—5.65 ppm (m) *CH=CH* 4 prot.
IR: 1680 cm^{-1} ν C=O
1705 cm^{-1} ν C=O

2) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 - dimethyl - (E) - 1 - buten - 1 - yl)] - pyrrolidone - 2

This product was obtained from 1 - (6 - methoxycarbonyl - (Z) - 2 - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 - dimethyl - (E) - 1 - buten - 1 - yl] - pyrrolidone - 2 according to Example 2 a_{VI}.
Chromatography: cyclohexane/ethyl acetate/glacial acetic acid (6:4:0.1).

NMR: δ=1.05 ppm (s) $C(CH_3)_2$ 6 prot.
δ=6.9—7.9 ppm (m) aromatic protons 8 prot.
IR: 1680 cm^{-1} ν C=O
1700 cm^{-1} ν C=O

3) 1 - (6 - Carboxyl - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 6 - pentafluoro - ethyl - (E) - 1 - hexen - 1 - yl) - pyrrolidone - 2

The product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-(3-hydroxy-6-pentafluoroethyl-(E)-1-hexen-1-yl)-pyrrolidone-2 according to Example 2 a_{VI}.
Chromatography: toluene/ethyl acetate/glacial acetic acid (5:4:0.1).

NMR: δ=5.2—5.45 ppm (m) *CH=CH* 4 prot.
IR: 1685 cm^{-1} ν C=O
1705 cm^{-1} ν C=O

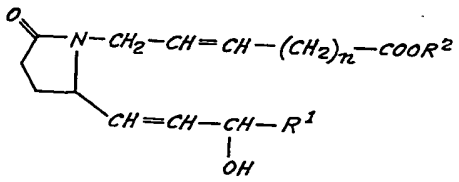
4) 1 - (6 - Carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - [3 - hydroxy - 5 - (4 - methyl - 2 - chlorophenyl) - 4,4 - dimethyl - (E) - 1 - penten - 1 - yl] - pyrrolidone - 2

This product was obtained from 1-(6-methoxycarbonyl-(Z)-2-hexen-1-yl)-5-[3-hydroxy-5-(4-methyl-2-chlorophenyl)-4,4-dimethyl-(E)-1-penten-1-yl]-pyrrolidone-2.
Chromatography: cyclohexane/ethyl acetate/glacial acetic acid (6:4:0.1).

NMR: δ=0.9 ppm (s) $C(CH_3)_2$ 6 prot.
δ=2.3 ppm (s) CH_3 3 prot.
δ=5.3—5.7 ppm *CH=CH* 4 prot.
IR: 1705 cm^{-1} ν C=O
1680 cm^{-1} ν C=O

WHAT WE CLAIM IS:—

1. A pyrrolidone of the formula I



(I)

in which

R^1 represents a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical having up to 10 carbon atoms, or a cycloaliphatic hydrocarbon radical having 3 to 7 carbon atoms, which radicals may be unsubstituted or substituted by one or more of the following:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 5 carbon atoms,

b) a phenoxy group which may carry one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms, optionally halogenated phenoxy groups, and alkoxy groups of 1 to 4 carbon atoms,

c) a furyloxy, thienyloxy or benzyloxy group which may carry, on the nucleus, one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms and alkoxy groups of 1 to 4 carbon atoms,

d) a trifluoromethyl or pentafluoroethyl group,

e) a cycloalkyl group of 3 to 7 carbon atoms,

f) a phenyl, thienyl or furyl group which may carry one or two substituents selected from optionally halogenated alkyl groups of 1 to 3 carbon atoms, halogen atoms, and alkoxy groups of 1 to 4 carbon atoms,

R^2 represents a straight or branched chain, saturated or unsaturated, aliphatic or cycloaliphatic hydrocarbon radical having up to 6 carbon atoms or an araliphatic hydrocarbon radical having 7 or 8 carbon atoms, and

n represents the integer two, three or four, and the corresponding free acid.

2. A compound as claimed in claim 1, wherein R^1 represents a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbon radical having up to 7 carbon atoms, or a cycloaliphatic hydrocarbon radical having 5 to 7 carbon atoms, which radicals may be unsubstituted or substituted by one or more of the following:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 4 carbon atoms,

b) a phenoxy group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, optionally halogenated phenoxy groups, and alkoxy groups of 1 or 2 carbon atoms,

c) a thienyloxy or benzyloxy group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, and alkoxy groups of 1 or 2 carbon atoms,

d) a trifluoromethyl group,

e) a cycloalkyl group of 5 to 7 carbon atoms,

f) a phenyl or thienyl group which may carry one or two substituents selected from alkyl groups of 1 to 3 carbon atoms, trifluoromethyl groups, halogen atoms, and alkoxy groups of 1 or 2 carbon atoms, and

R^2 represents a straight or branched chain alkyl group of 1 to 6 carbon atoms, a straight or branched chain alkenyl group of 2 to 4 carbon atoms, a cycloalkyl group of 5 or 6 carbon atoms, or an aralkyl group of 7 or 8 carbon atoms.

3. A compound as claimed in claim 1, wherein

R^1 represents a straight or branched chain alkyl group of 1 to 7 carbon atoms, a straight or branched chain alkenyl group of 3 to 5 carbon atoms, or a cycloalkyl group of 5 to 7 carbon atoms, which may be unsubstituted or substituted by one or more of the following:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio group of up to 3 carbon atoms,

b) a phenoxy group which may carry one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and optionally chlorinated or fluorinated phenoxy groups,

c) a thienyloxy or benzyloxy group which may carry in its nucleus ne or

two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

d) a trifluoromethyl group,

e) a cycloalkyl group of 5 to 7 carbon atoms,

f) a phenyl or thienyl group which may carry one or two substituents selected from methyl, trifluoromethyl and methoxy groups, chlorine and or fluorine atoms and

R^2 represents a straight chain alkyl group of 1 to 6 carbon atoms, a branched alkyl group of 3 to 5 carbon atoms, a straight-chained alkenyl group of 2 to 4 carbon atoms, a cyclopentyl or cyclohexyl group, or a benzyl group.

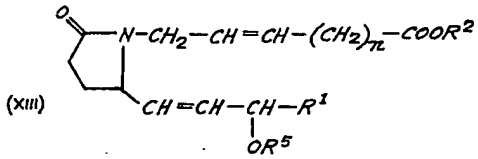
4. A compound as claimed in claim 1 and which is named in Table A herein.

5. A compound as claimed in claim 1 and which is named in Example 2 or Example 6 herein.

6. A salt of a free acid as claimed in any one of claims 1 to 5.

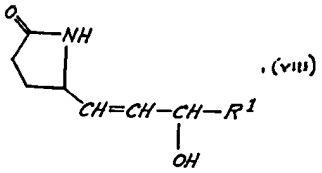
7. A physiologically tolerable salt of a free acid as claimed in any one of claims 1 to 5.

8. A process for the manufacture of a pyrrolidone of formula I as claimed in claim 1, which comprises splitting off the group represented by R^5 in a compound of the formula XIII



(XIII)

in which R^1, R^2 and n are defined as above, R^2 may also represent hydrogen, and R^5 represents a protective group which can be split off easily under acid conditions, or deprotonizing a compound of the formula VIII

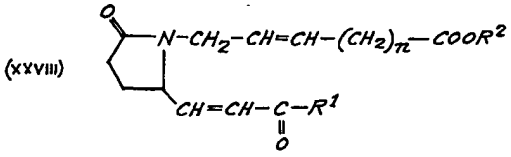


(VIII)

in which R^1 is defined as above, at the nitrogen atom by means of a base, and reacting the resulting anion with a compound of the formula XII

$$Y—CH_2—CH=CH—(CH_2)_n—COOR^2 \qquad XII$$

in which R^2 and n are defined as above, R^2 may be also represent hydrogen, and Y represents a radical which may be substituted by a nucleophilic substitution reaction, or in a compound of the formula XXVIII

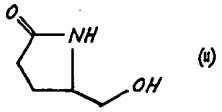


(XXVIII)

in which R^1, R^2 and n are defined as above, and R^2 may also represent hydrogen, reducing the ketocarbonyl group, and optionally converting a resulting compound of formula I into the corresponding free acid, or a salt, ester or another ester thereof, as appropriate.

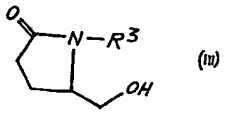
9. A process for the manufacture of a pyrrolidone of formula I as claimed in claim 1, wherein

a_1) a pyrrolidone of the formula II



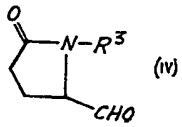
(II)

is protected at the nitrogen atom by introducing a protective group (R^3) which can easily be split off, to yield a pyrrolidone of the formula III



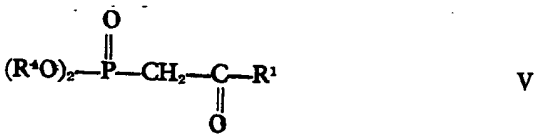
(III)

a_2) the pyrrolidone of formula III is oxidized to yield an aldehyde of the formula IV



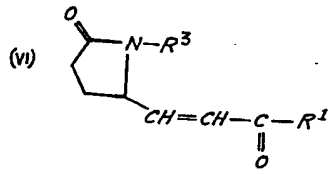
(IV)

a_3) the so-obtained aldehyde of formula IV is reacted with a phosphonate of the formula V



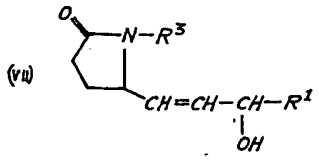
V

in which R^1 is defined as above, and R^4 represents an unbranched alkyl group of 1 to 4 carbon atoms, to yield a compound of the formula VI



(VI)

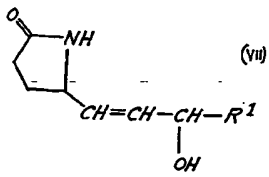
a_4) in the so-obtained compound of formula VI, the ketocarbonyl group is reduced to yield a compound of the formula VII



(VII)

in which R^1 is defined as above,

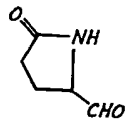
a_5) in the compound of formula VII, the protective group linked to the nitrogen atom is split off to yield a compound of the formula VIII



(VIII)

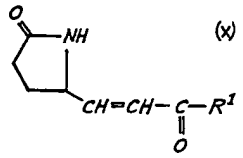
in which R^1 is defined as above, or

a_{5_1}) the pyrrolidone of formula II is oxidized to yield an aldehyde of the formula IX



(IX)

a_{5_2}) th so-obtained aldehyde of formula IX is reacted with a phosphonate of formula V to yield a compound of the formula X



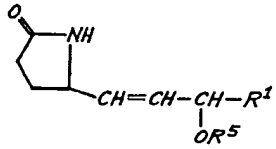
(X)

in which R^1 is defined as above, or

$a_{5'_2}$) in a compound of formula VI, the protective group linked to the nitrogen atom is split off to yield a compound of formula X,

a_{5_3}) in a compound of formula X, the ketocarbonyl group is reduced to yield a compound of formula VIII,

a_6) the alcohol function in a compound of formula VIII is protected with a group which can easily be split off under acid conditions, to yield a compound of the formula XI



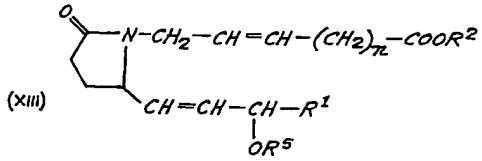
(XI)

in which R^1 is defined as above, and R^5 represents a protective group which can be easily split off under acid conditions,

a_7) the pyrrolidone of formula XI is deprotonized with a base at the nitrogen atom, and the resulting anion is reacted with a carboxylic acid derivative of the formula XII

$$Y—CH_2—CH=CH—(CH_2)_n—COOR^2 \qquad XII$$

in which R^2 and n are defined as above, and Y represents a radical which can be substituted by a nucleophilic substitution reaction, to yield a compound of the formula XIII



(XIII)

in which R^1, R^2 and n are defined as above, and R^5 represents a protective group, in which can be easily split off under acid conditions, the resulting ester is optionally hydrolyzed to yield the corresponding acid of formula XIII, in which R^2 represents hydrogen,

a_8) the alcohol protective group R^5 in the compound of formula XIII is split off to yield a compound of formula I, and this compound is optionally converted into the corresponding free acid or a salt thereof, or

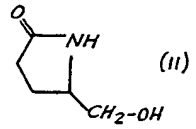
$a_{8'}$) the compound of formula VIII is deprotonized with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield directly a compound of formula I, or

a_{7_1}) the pyrrolidone of formula XI is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 is hydrogen, to yield a compound of formula XIII, in which R^2 is hydrogen, and the resulting acid is optionally converted into an ester of formula XIII,

a_{8_1}) the alcohol protective group in a compound of formula XIII, in which R^2 is hydrogen, is split off to yield a compound of formula I, in which R^2 is hydrogen, and this acid is optionally converted into a salt or an ester thereof, or

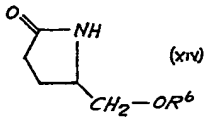
$a_{8_{1'}}$) the compound of formula VIII is deprotonized with a base, and the resultanion is reacted with a carboxylic acid derivative of formula XII, in which R^2 is hydrogen, to yield directly a compound of formula I (R^2=H), or

b_1) in a pyrrolidone of the formula II



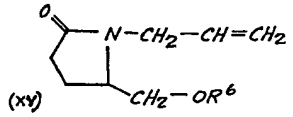
(II)

an alcohol protective group R^6, which can be easily split off under acid conditions, is introduced to yield a compound of the formula XIV



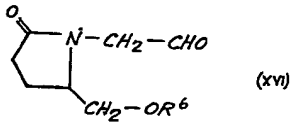
(XIV)

b_2) the pyrrolidone of formula XIV is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with an allyl halide to yield a pyrrolidone of the formula XV



(XV)

b_3) the so-obtained pyrrolidone of formula XV is ozonolyzed to yield an aldehyde of the formula XVI

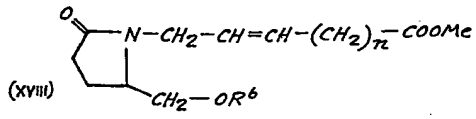


(XVI)

b_4) the so-obtained aldehyde of formula XVI is reacted with an ylide of the formula XVII

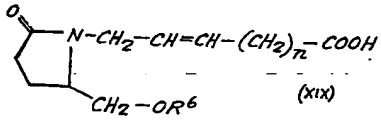
$$(R^7)_3P=CH(CH_2)_nCOOMe \qquad \text{XVII}$$

in which n is defined as above, R^7 represents identical or different groups selected from straight chain alkyl groups of 1 to 4 carbon atoms and phenyl groups, and Me represents an alkali metal ion, to yield a compound of the formula XVIII



(XVIII)

and this compound is treated to set free the corresponding acid of the formula XIX

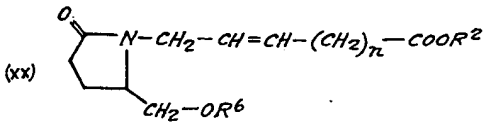


(XIX)

in which formulae XVIII and XIX, n is defined as above, or

$b_{4'}$) the protected pyrrolidone of formula XIV is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 is hydrogen, to yield a compound of formula XIX,

b_5) the so-obtained compound of formula XIX is converted into the corresponding ester of the formula XX

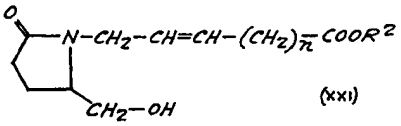


(XX)

in which R^2 and n are defined as above, or

$b_{5'}$) the protected pyrrolidone of formula XIV is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield directly a compound of formula XX,

b_6) the protective group R^6 in the so-obtained compound of formula XX is split off under acid conditions to yield an alcohol of the formula XXI



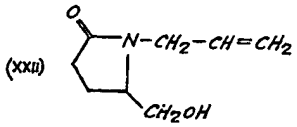
(XXI)

in which R^2 and n are defined as above, and then the corresponding acid is optionally set free, or

$b_{6'}$) esterification of a compound of formula XIX as well as the splitting-off reaction of the protective group R^6 are carried out in a single step, or

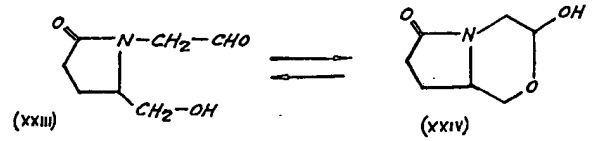
$b_{6''}$) the pyrrolidone of formula II is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield directly a compound of formula XXI, or

b_{6_1}) the pyrrolidone of formula II is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with an allyl halide to yield a compound of the formula XXII



(XXII)

b_{6_2}) the so-obtained compound of formula XXII is ozonolyzed to yield a compound of the formula XXIII or the cyclisized tautomer of the formula XXIV thereof

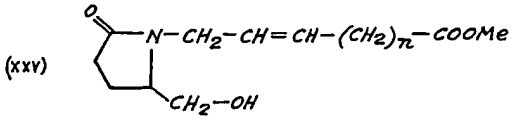


(XXIII) (XXIV)

or

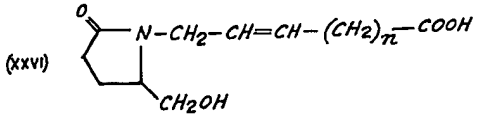
$b_{6_{2'}}$) in a compound of formula XVI, the protective group R^8 is split off to yield also a compound of formula XXIII or XXIV,

b_{6_3}) the compound of formula XXIII or XXIV is reacted with an ylide of formula XVII to yield a compound of the formula XXV



(XXV)

which is treated to set free the corresponding acid of the formula XXVI



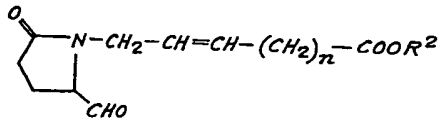
(XXVI)

and this acid is optionally converted into an ester of formula XXI, n in the formulae XXV and XXVI being defined as above, or

$b_{6_{3'}}$) the pyrrolidone of formula II is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII, in which R^2 is hydrogen, or

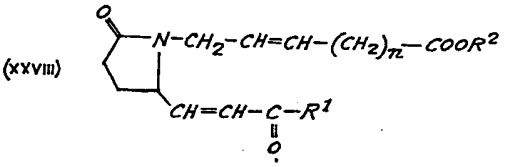
$b_{6_{3''}}$) in a compound of formula XIX the protective group R^6 is split off to yield a compound of formula XXVI,

b_7) the so-obtained alcohol of formula XXI is oxidized to yield an aldehyde of the formula XXVII

(XXVII) 

in which R^2 and n are defined as above, and optionally the corresponding acid of formula XXVII (R^2=H) is set free therefrom,

b_8) the so-obtained aldehyde of formula XXVII is reacted with a phosphonate of formula V to yield a compound of the formula XXVIII

(XXVIII) 

in which R^1, R^2 and n are defined as above, or

$b_{8'}$) a compound of formula X is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII to yield a compound of formula XXVIII,

b_9) in the so-obtained compound of formula XXVIII, the ketocarbonyl group is reduced to yield a compound of formula I, and this compound is optionally converted into the corresponding free acid or a salt thereof, or

b_{7_1}) a compound of formula XXVI is oxidized to yield an aldehyde of formula XXVII, in which R^2 is hydrogen, and this aldehyde is optionally converted into an ester of formula XXVII, or

b_{8_1}) an aldehyde of formula XXVII, in which R^2 is hydrogen, is reacted with a phosphonate of formula V to yield a compound of formula XXVIII (R^2=H), and this compound is optionally converted into an ester of formula XXVIII, or

$b_{8_{1'}}$) a compound of formula X is deprotonized at the nitrogen atom with a base, and the resulting anion is reacted with a carboxylic acid derivative of formula XII (R^2=H) to yield directly a compound of formula XXVIII (R^2=H),

b_{9_1}) in a compound of formula XXVIII, in which R^2 is hydrogen, the ketocarbonyl group is reduced, and the resulting compound of formula I (R^2=H) is optionally converted into a salt or an ester thereof.

10. A process as claimed in claim 8 or claim 9, carried out substantially as described in Example 2 or Example 6 herein.

11. A compound of formula I as claimed in claim 1 the free acid or a salt thereof, whenever produced by a process as claimed in any one of claims 8 to 10.

12. A pharmaceutical preparation which comprises a compound of formula I as claimed in any one of claims 1 to 5, the free acid thereof, a physiologically tolerable salt thereof or a mixture of two or more such compounds, acids and salts, as active ingredient in admixture or conjunction with a pharmaceutically suitable carrier.

13. A pharmaceutical preparation as claimed in claim 12, in a form suitable for injection or infusion.

14. A pharmaceutical preparation as claimed in claim 13, in unit dosage form.

15. A pharmaceutical preparation as claimed in claim 14, which comprises from 5 to 5,000 mg of the active ingredient per unit dose.

16. A pharmaceutical preparation as claimed in claim 15, which comprises from 5 to 500 mg of the active ingredient per unit dose.

17. A pharmaceutical preparation as claimed in claim 12, in a form suitable for oral administration.

18. A pharmaceutical preparation as claimed in claim 17, in unit dosage form.

19. A pharmaceutical preparation as claimed in claim 18, which comprises from 1 to 100 mg of the active ingredient per unit dose.

20. A pharmaceutical preparation as claimed in claim 19, which comprises from 1 to 50 mg of the active ingredient per unit dose.

21. A pharmaceutical preparation as claimed in claim 12, in a form suitable for local administration.

22. A pharmaceutical preparation as claimed in claim 21 in the form of a cream, emulsion or suppository.

23. A pharmaceutical preparation as claimed in claim 21, in the form of a spray.

24. A pharmaceutical preparation as claimed in claim 23, wherein the spray is capable of administering unit doses of the active ingredient.

25. A pharmaceutical preparation as claimed in claim 24, wherein the unit dose comprises from 0.3 to 3,000 mg of the active ingredient.

26. A pharmaceutical preparation as claimed in claim 25, wherein the unit dose comprises from 3 to 600 mg of the active ingredient.

27. A pharmaceutical preparation as claimed in any one of claims 12 to 26, which also comprises one or more further active ingredients.

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